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PETITION FEE
Under 37 CFR 1.17(f), (g) & (h)
TRANSMITTAL

(Fees are subject to annual revision)

Send completed form to: Commissioner for Patents
P.O. Box 1450, Alexandria, VA 22313-1450

Application Number	10/587,246-Conf. #9704
Filing Date	July 6, 2007
First Named Inventor	Yutaka UMEHARA
Art Unit	1797
Examiner Name	Sun U. Kim
Attorney Docket Number	4600-0124PUS1

Enclosed is a petition filed under 37 CFR 1.182 **that requires a processing fee (37 CFR 1.17(f), (g), or (h)). Payment of $** 400.00 **is enclosed.**

This form should be included with the above-mentioned petition and faxed or mailed to the Office using the appropriate Mail Stop (e.g., Mail Stop Petition), if applicable. *For transmittal of processing fees under 37 CFR 1.17(i), see form PTO/SB/17i.*

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Petition Fees under 37 CFR 1.17(f): Fee $400 Fee Code 1462

For petitions filed under:
§ 1.36(a) – for revocation of a power of attorney by fewer than all applicants
§ 1.53(e) – to accord a filing date.
§ 1.57(a) – to accord a filing date.
§ 1.182 – for decision on a question not specifically provided for.
§ 1.183 – to suspend the rules.
§ 1.378(e) – for reconsideration of decision on petition refusing to accept delayed payment of maintenance fee in an expired patent.
§ 1.741(b) – to accord a filing date to an application under § 1.740 for extension of a patent term.

Petition Fees under 37 CFR 1.17(g): Fee $200 Fee Code 1463

For petitions filed under:
§ 1.12 – for access to an assignment record.
§ 1.14 – for access to an application.
§ 1.47 – for filing by other than all the inventors or a person not the inventor.
§ 1.59 – for expungement of information.
§ 1.103(a) – to suspend action in an application.
§ 1.136(b) – for review of a request for extension of time when the provisions of section 1.136(a) are not available.
§ 1.295 – for review of refusal to publish a statutory invention registration.
§ 1.296 – to withdraw a request for publication of a statutory invention registration filed on or after the date the notice of intent to publish issued.
§ 1.377 – for review of decision refusing to accept and record payment of a maintenance fee filed prior to expiration of a patent.
§ 1.550(c) – for patent owner requests for extension of time in ex parte reexamination proceedings.
§ 1.956 – for patent owner requests for extension of time in inter partes reexamination proceedings.
§ 5.12 – for expedited handling of a foreign filing license.
§ 5.15 – for changing the scope of a license.
§ 5.25 – for retroactive license.

Petition Fees under 37 CFR 1.17(h): Fee $130 Fee Code 1464

For petitions filed under:
§ 1.19(g) – to request documents in a form other than that provided in this part.
§ 1.84 – for accepting color drawings or photographs.
§ 1.91 – for entry of a model or exhibit.
§ 1.102(d) – to make an application special.
§ 1.138(c) – to expressly abandon an application to avoid publication.
§ 1.313 – to withdraw an application from issue.
§ 1.314 – to defer issuance of a patent.

Signature	FEB 07 2008 Date
Gerald M. Murphy, Jr. Typed or printed name	28,977 Registration No., if applicable

Docket No.: 4600-0124PUS1
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Yutaka UMEHARA et al.

Application No.: 10/587,246 | Confirmation No.: 5271

Filed: July 6, 2007 | Art Unit: 1797

For: PLASMA EXCHANGE WASTE LIQUID PURIFICATION AND CIRCULATION DIALYSIS APPARATUS | Examiner: Sun U. Kim

PETITION UNDER 37 CFR 1.182

Assistant Commissioner for Patents
Mail Stop PCT
P.O. Box 1450
Alexandria, VA 22313-1450
ATTN: OFFICE OF PCT LEGAL ADMINISTRATION

Sir:

In response to the Decision dated January 8, 2008 (copy attached), the following remarks are submitted.

The Examiner notes that the declaration filed on May 1, 2007 in connection with the above-identified patent application "nominates an inventor (Mutsuo SASAKI) in place of "Sasaki mutsuo" nominated in the published international application." The Examiner further notes that "[i]n that this is clearly more than a mere typographical error or phonetic misspelling of applicants' name (because of the change in the order of the names), a proper petition...is required to resolve this discrepancy".

Petitioners hereby request that the declaration filed on May 1, 2007 in connection with the above-identified patent application be accepted as filed despite the discrepancy noted by the Examiner.

The Examiner's attention is respectfully directed to the cover page of International Application WO 2005/070478A1 (copy attached), reference number (75). Petitioners respectfully submit that the International Application identifies inventors' names in the following order: Family Name/Given Name (e.g., UMEHARA, Yutaka; UMEHARA, Minoru). Accordingly, it follows that the name "Sasaki mutsuo" identifies the inventor by his Family Name (Sasaki)/Given Name (mutsuo). This information is in accordance with information supplied on the declaration filed on May 1, 2007 in the above-identified application ("Mutsuo SASAKI", wherein "Mutsuo" represents the Given Name and "SASAKI" represents the Family Name).

The reason why the Family Name of inventor Sasaki was not capitalized (e.g., "SASAKI") and a comma was not inserted between the inventor's Family Name and Given Name is not clear to Petitioners. However, Petitioners submit that these errors are typographical errors in the International Application as published.

Furthermore, Petitioners submit herewith a copy of EP 1 709 982 A1 (copy attached), as further evidence that the inventor's name on the declaration filed on May 1, 2007 in the above-identified application is accurate and correct.

Petitioners respectfully submit that declaration filed on May 1, 2007 in the above-identified application is not defective, and further submit that a new oath or declaration is not necessary. Petitioners request that the USPTO accepts the declaration filed on May 1, 2007 in

connection with the above-identified patent application despite the discrepancy noted by the Examiner.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to Gerald M. Murphy, Jr., Reg. No. 28,977 at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.14; particularly, extension of time fees.

Dated: FEB 07 2008

Respectfully submitted,

By _____
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Attachments: Copy of Decision dated January 8, 2008
Copy of WO 2005/070478 A1
Copy of EP 1 709 982 A1

GMM/VP/sh

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COPY

DOCKETED
Response due
2-8-08

In re Application of
Umehara et al.
Application No.: 10/587,246 (11/742,676)
PCT No.: PCT/JP2005/000825
Int'l Filing Date: 24 January 2005
Priority Date: 27 January 2004
Attorney Docket No.: 4600-0124PUS1
For: Plasma Exchange Waste Liquid Purification And Circulation Dialysis Apparatus

DECISION

This is in response to the renewed petition under 37 CFR 1.182 filed on 30 November 2007 and directed to application no. 11/742,676, which requests that documents submitted in 11/742,676 be placed into the instant application, no. 10/587,246.

DISCUSSION

In a Decision mailed on 01 October 2007 (and addressed to 11/742,676), the correspondence filed on 06 July 2007 was treated as a petition under 37 CFR 1.182 and dismissed, without prejudice, because

> *Petitioner has not unambiguously described the relief sought. Specifically, petitioner variously suggests that the declaration was intended to be filed in application 10/582,246 or 10/587,246, but does not request that the declaration (or any of the correspondence filed on 01 May 2007) be placed into one of those applications. Instead, petitioner merely urges that the declaration and response "should have been" filed in 10/587,246 (or perhaps 10/582,246) but requests only that they "be removed from the above-identified application." Thus, it is uncertain if petitioner is affirmatively seeking incorporation into another application (whether 10/582,246 or 10/587,246) of the correspondence placed into the instant application, or merely removal of papers from the instant case. Clarification is required.*
>
> *Petitioner has not clearly defined the manner in which the discrepancy described in the petition arose. Though petitioner states that he "has first hand knowledge of the facts associated with the present situation," it is not clear that he was the individual who committed the "clerical error." If not, a statement from the appropriate person would be appropriate. Also, it is not clear exactly what "clerical error" occurred. For instance, was the error made at the point of the selection of options while electronically filing the correspondence, or did applicants mistakenly decide to file the papers into a new application ("duplicate application 11/742,676 was intended to be...)? Petitioner should more clearly define the nature and timing of the "clerical error," identify who committed the error, and provide a statement by that individual.*

In response, petitioner more clearly explains that, on 01 May 2007, applicants attempted to e-file documents into the instant application in response to a Notification of Missing Requirements mailed on 09 April 2007. However, due to what is described as an inadvertent error on the part of a secretary who is no longer in counsel's employ, the documents in question were instead filed as a "new application" which was assigned application no. 11/742,676. Accordingly, "petitioner requests that all correspondence filed on May 1, 2007, which the USPTO associated with new Application No. 11/742,676, be removed from said file and incorporated into Application No. 10/587,246, as originally intended. Petitioner has expressly abandoned Application No. 11/742,676." Based on the totality of the circumstances presented, it would be appropriate to grant the requested relief. Accordingly, copies of the correspondence in question (including a declaration document, a Response to Notification of Defective Response, a copy of the Notification of Defective Response mailed on 09 April 2007, as well as the associated Electronic Acknowledgement Receipt) from 11/742,676 are being placed into the instant application, no. 10/587,246. All further correspondence with respect to this matter should be directed to 10/587,246.

It is noted that the declaration filed on 01 May 2007 nominates an inventor (Mutsuo SASAKI) in place of "Sasaki mutsuo" nominated in the published international application. In that this is clearly more than a mere typographic error or phonetic misspelling of applicants' name (because of the change in the order of the names), a proper petition (under 37 CFR 1.182) is required to resolve this discrepancy. *See* MPEP 605.04(b).

CONCLUSION

The petition is **GRANTED** to the extent noted above.

Petitioner is required to file a proper response (i.e., either a new oath or declaration compliant with 37 CFR 1.497(a) and (b) or else a grantable petition to accept the declaration as filed on 01 May 2007 despite the discrepancy noted above) within **ONE (1) MONTH** of the mailing date of this Decision. Extensions of time under 37 CFR 1.136(a) are **NOT** available. Failure to timely reply will result in **ABANDONMENT**.

Please direct any further correspondence with respect to this matter to the Assistant Commissioner for Patents, Mail Stop PCT, P.O. Box 1450, Alexandria, VA 22313-1450, and address the contents of the letter to the attention of the Office of PCT Legal Administration.

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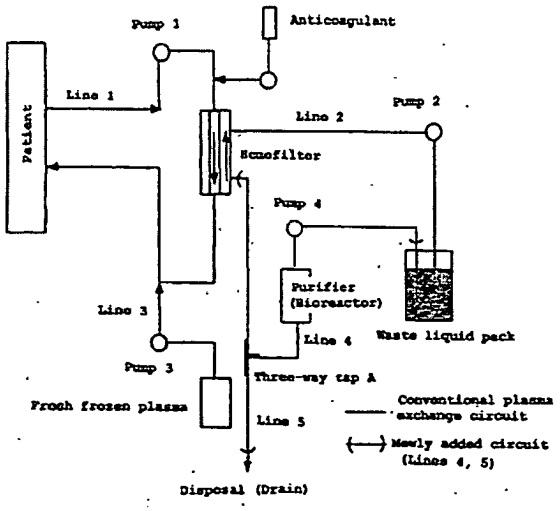
(54) PLASMA EXCHANGE WASTE LIQUID PURIFICATION CIRCULATION DIALYZER

(57) The object of the invention is to provide an apparatus used in a plasma exchange therapy, which is operable with only a minor modification to a conventional plasma exchange apparatus and wherein valuable plasma is not disposed but recycled as a dialysis solution.

The present invention is related to an apparatus used in a plasma exchange therapy wherein at least a portion of separated plasma is purified and circulated as a dialysis solution to dialyze patient's blood to remove harmful substances contained in the plasma; a plasma exchange apparatus incorporating said apparatus; and an artificial liver equipped with these apparatuses.

FIG. 1



EP 1 709 982 A1

Printed by Jouve, 75001 PARIS (FR)

Description

FIELD OF THE INVENTION

[0001] The invention relates to a plasma exchange waste liquid purification and circulation dialysis apparatus wherein at least a portion of plasma separated from a patient is purified and circulated as a dialysis solution to dialyze the patient's blood to remove harmful substances contained in the plasma.

BACKGROUND ART

[0002] A plasma exchange therapy (plasma separation and exchange therapy) wherein patient's plasma is replaced by fresh and frozen plasma obtained from a normal individual will be adopted when other kinds of therapy demonstrated no or insufficient effect for disorders caused by an abnormal antibody, an immuno-complex or an overproduced normal factor such as, for example, acute hepatic insufficiency, anti-glomerular basement membrane antibody diseases such as Goodpasture syndrome, amyosthenia, Guillain-Barre syndrome, necrotizing angitis, thrombopenic purpura thrombotic, and familial cholesteremia.

[0003] Representative examples of said plasma exchange therapy are listed as follows:

[Simple plasma exchange therapy]

[0004] It is impossible to infuse fresh plasma after the removal of all of the plasma components, which would mean "exchange" in a true sense, due to the necessity of maintenance of body function. Accordingly, hematocytes and plasma are separated by centrifugal force applied at a hemofilter or plasma separator, and the fresh and frozen plasma will be infused while the patient's plasma thus separated being disposed. However, since the patient' s plasma will always be separated and disposed only after having been mixed with the infused fresh plasma in body, it is presumed that the composition of the patient's plasma after the exchange of a certain amount of plasma will be almost the same as that of the plasma disposed. That is to say, this "plasma exchange therapy" is actually no more than dilution of the patient's plasma with a certain amount of the fresh plasma, and disposal of surplus of the plasma.

[Double-filtration plasma exchange therapy]

[0005] This method removes plasma proteins more selectively than in the simple plasma exchange therapy, and recycles a portion of the plasma and uses an albumin solution as a supplementing liquid. However, as it requires separation by means of molecular weight fraction, there is a possibility that necessary proteins may be removed as well.

[0006] The following "Plasma adsorption therapy" and "MARS" may be also mentioned as representative examples of the method for removing disease agent and toxic substances in plasma.

[Plasma adsorption therapy]

[0007] Almost all kinds of adsorbents will require perfusion in a plasma state for fear of blood clot, decrease of platelets and hemolysis. It is therefore the plasma will be in contact with an adsorbent after it is separated from hematocytes so that disease agent in the plasma may be selectively removed. However, this therapy has to be sometimes combined with the simple plasma exchange therapy depending on conditions such as in acute hepatic insufficiency. Accordingly, a therapy that can be more simply combined with other kinds of therapy is required for view of complexity of apparatuses and complication of procedures.

[Molecular Adsorbent Recycling System ("MARS" trade mark)]

[0008] This was developed for the purpose of selectively removing protein-binding toxic substances using the albumin solution as the dialysis solution in the treatment of acute hepatic insufficiency. Random sampling tests are currently conducted in facilities mainly in Germany and France. The removing efficiency greatly depends on a dialysis membrane, as the toxic substances binding to the albumin can permeate it while albumin itself cannot permeate the membrane. Since there is an objection to a concept of this therapy, it seems that it will take more time for the therapy to be recognized as a new technology.

Non-Patent document 1 :
Umehara, et al., LIVERAID TM-A Novel Hybrid Bioartificial Liver-Hepatology 2002, 36(4) suppl.:681A
Non-Patent document 2 :

Watanabe et al. , Clinical experience with a bioartificial liver in the treatment of severe liver failure- A pahse I clinical Trial- Annals of Surgery 1997: 225 (5): 484-494

Non-Patent document 3 :

Stange, et al., Molecular Adsorbent Recycling System (MARS) : Clinical results of a new membrane based blood purification system for bioartificial liver suppport, Artif Organs 1999:23 (4):319-330

SUMMARY OF THE INVENTION

PROBLEMS TO BE SOLVED BY THE INVENTION

[0009] All of the fresh and frozen plasma is supplied from blood donated by volunteers now in Japan. Accordingly, a method to utilize more effectively such valuable material obtained from human body in the plasma exchange therapy.

[0010] The present inventors have studied hard to solve the above problems, and finally found that plasma exchange waste liquid (separated plasma) may be utilized in a secondary therapy, more specifically used as a dialysis solution after being purified. The present invention was made on the basis of the above findings.

MEANS FOR SOLVING THE PROBLEM

[0011] Thus, the present invention relates to a plasma exchange waste liquid purification and circulation dialysis apparatus wherein at least a portion of separated plasma is purified and circulated as a dialysis solution to dialyze patient's blood to remove harmful substances contained in the plasma. As already mentioned above, the representative examples of the plasma exchange therapy include the simple plasma exchange therapy and double-filtration plasma exchange therapy. The apparatus according to the present invention may be used widely in any plasma exchange therapy in addition to the above methods.

[0012] In one example, the apparatus comprises a purifier and dialyzer as their constituent elements. Dialysis of patient's blood with the separated plasma circulated through the dialyzer may be performed by any means or method known for those skilled in the art. The dialyzer (dialysis apparatus) may be equipped independently from an apparatus for plasma separation such as a plasma separator or hemofilter that are used in the plasma exchange, or more conveniently the apparatus for plasma separation may function also as the dialyzer..

[0013] Purification of the separated plasma may be preformed at the purifier (bioreactor) by any means or method known for those skilled in the art. Various harmful substances such as disease agents and toxic substances can be removed from the separated plasma by the purifier. For example, when the purifier is composed of an adsorption separator, various harmful substances binding to the plasma proteins will be adsorbed to any adsorbent equipped with the adsorption separator and removed from the plasma by the action of adsorbents such as various ion-exchange resins; various porous copolymers synthesized from divinyl-benzene, divinyl-toluene and styrene; activated carbon; and alumina.

[0014] A preferable example of the present invention may be so constructed that the separated plasma functions as reservoir of the dialysis solution. The apparatus of the present invention may comprise other elements known for those skilled in the art, such as a pump, a line and a three-way tap. One example of the apparatus of the present invention is composed of a hemofilter, a purifier, a three-way tap, a pump (4), a line (4) and a line (5) shown in Fig.1.

[0015] The plasma exchange waste liquid purification and circulation dialysis apparatus according to the present invention may be easily added to any type of the plasma exchange apparatuses and used as a part thereof. It is therefore that the present invention relates also to a plasma exchange apparatus incorporating the plasma exchange waste liquid purification and circulation dialysis apparatus of the present invention.

[0016] An artificial liver using liver cells or tissue is now being developed in order to be used in the treatment of acute hepatic insufficiency or as an intermediary for liver transplantation. Many of them adopt a system wherein plasma is separated, oxygenated, and induced into a bioreactor, mixed with hematocytes and brought back into a patient's body. It has been reported that the plasma of the patient suffering from acute hepatic insufficiency comprises components that will impair the function of the liver cells or tissue. It seems therefore very effective that the concentration of the above harmful substances is decreased by means of the plasma exchange therapy before the treatment using the bioreactor with the liver cells or tissue.

[0017] The present invention is therefore related to an artificial liver including a hybrid type equipped with the plasma exchange waste liquid purification and circulation dialysis apparatus of the present invention. Such artificial liver may serve as a platform for various types of the bioreactor in the development of the artificial liver.

ADVANTAGES OF THE INVENTION

[0018] It is possible to effectively remove the harmful substances contained in the plasma by recycling the plasma as the dialysis solution without being disposed with the use of the apparatus according to the present invention. Furthermore,

as the apparatus of the present invention is operable with only a minor modification to a conventional plasma exchange apparatus, other therapy such as the plasma adsorption therapy can be quickly initiated after the simple plasma exchange therapy is finished. Priming volume of an apparatus will often make some problems in blood purification therapy. However, since the plasma exchange waste liquid may function as reservoir of the dialysis solution and a priming solution in the apparatus of the present invention, it can be used very safely even for patients who are instable in circulatory dynamics or have small body such as children.

BRIEF DESCRIPTION OF DRAWINGS

[0019]

Fig.1 shows an example of the present apparatus.
Fig.2 shows a circuit of the example at the time of plasma exchange (PE).
Fig.3 shows a circuit of the example at the time of priming by plasma exchange waste liquid of the purifier.
Fig.4 shows a circuit of the example at the time of plasma exchange waste liquid purification and circulation dialysis (Plasma Recycling Dialysis:PRD).
Fig.5 is a graph showing changes in the value of a total bile acid (TBA) in the plasma and the plasma exchange waste liquid at 0.5, 1 and 2 hours after the initiation of the plasma exchange (PE). The value in the plasma before PE is set as "100" and the other values are shown as % for said value.
Fig.6 is a graph showing changes in the value of a total bilirubin(T-Bil) in the plasma and the plasma exchange waste liquid at 0.5, 1 and 2 hours after the initiation of the plasma exchange (PE). The value in the plasma before PE is set as "100" and the other values are shown as % for said value.
Fig.7 is a graph showing changes in blood pressure (Systolic pressure) before or after the transition from PE to PRD.
Fig.8 is a graph showing changes in the number of white blood cell (WBC) through PE and PRD.
Fig. 9 is a graph showing changes in the number of red blood cell (RBC) through PE and PRD.
Fig.10 is a graph showing changes in the value of hemoglobin (Hb) through PE and PRD.
Fig.11 is a graph showing changes in the value of hematocrit (Ht) through PE and PRD.
Fig.12 is a graph showing changes in the number of platelet through PE and PRD.
Fig.13 is a graph showing changes in the value of TBA through PE and PRD.
Fig.14 is a graph showing changes in the value of T-Bil through PE and PRD.

EXPLANATION OF SYMBOLS

[0020]

1: Pump, Line;
2: Pump, Line;
3: Pump, Line;
4: Pump, Line;
5: Line;
6: Plasma separator;
7: Purifier (anion-exchange resin)

Best Mode for Carrying out the Invention

[0021] One example of the present invention will be explained with reference to Fig.1. The numbers in the specification correspond to those in the figure. Those skilled in the art may easily conceive various aspects having the technical features of the present invention based on the disclosure of the present specification and technical common sense in the art, and it is clear and obvious that such various aspects shall therefore fall within the scope of the present invention.

[0022] Patient's blood is first introduced (100 ml/min) into the hemofilter (that will serve also as the dialyzer) through a line (1) by means of a pump (1). The plasma exchange waste liquid is separated and passed (5-10 ml/min) through a pump (2) to a waste liquid pack. Simultaneously, fresh frozen plasma (FFP) is perfused into the patient at the same rate through a line (3) by means of a pump (3). A pump (4) is stopped, and lines (4) and (5) are closed with a three-way tap (A) during the above procedures. After a predetermined amount of the plasma has been exchanged, the pumps (2) and (3) are stopped, and the lines (4) and (5) are opened, and then a predetermined amount of the plasma exchange waste liquid in the waste liquid pack is disposed through the line (5) by means of the pump (4). For example, one (L) of the plasma exchange waste liquid out of 2 (L) in total is disposed and the other one(L) is left in the waste liquid pack (Priming by the plasma exchange waste liquid of the line (4) and the purifier). The line (5) is then closed by the three-

way tap (A). The pumps (2) and (4) are then rotated at the same rate (for example, 400 ml/min) to purify the plasma exchange waste liquid and dialyze the plasma.

[0023] Any element known for those skilled in the art may be used as the constituent elements used in the above apparatus, such as the apparatus for plasma separation (the plasma separator or hemofilter), the pump, and the line. Furthermore, those skilled in the art may use or operate the apparatus shown in Fig.1 without any difficulty.

EXAMPLE

[0024] Examples of the plasma exchange and the plasma exchange waste liquid purification and circulation dialysis (Plasma Recycling Dialysis:PRD) with the apparatus according to the present invention shall be shown by an animal experiment using a hyper-bilirubin plasma pig model. The following examples will not limit in any sense the scope of the present invention.

Method

[Experimental animal]

[0025] A fatted female pig (25-30 kg body weight) was bred in a metal breeding gauge for the experiment. The animal was bred under sunshine of from eight to twenty o'clock at a constant temperature and humidity (22±2 °C, 55±10%) and free to take tap water. All of the experiment were conducted in accordance with "Guideline for animal experiments at Hirosaki University." All of the operations and extracorporeal circulation were done under general anesthesia as follows. The animal was fasted except free uptake of water from the night before the operation. Ketamine (15 mg/kg) and Atropine (0.01 mg/kg) were intramuscularly injected. After the pig had fallen asleep, a blood vessel was secured from an auricular vein. After thiopentanol sodium (100mg) was administered, intratracheal intubation was done. Anesthesia was kept by administrating Midazolam (0.3 mg/kg/h), Pentazocine (0.3 mg/kg/h) and pancuronium bromide (0.4 mg/kg/h) under artificial respiration using a ventilator

Hyper-bilirubin plasma pig model

[0026] The pig model was prepared under general anesthesia by subjecting to an abdominal operation at median and upper abdomen, extracting a gall bladder, and ligating and cutting of choledoch duct (common bile duct). The course after the operation was observed while the animal was bred in the gauge. Seven days later, under general anesthesia, a double lumen catheter for extracorporeal circulation (GamCath, Gambro, Stockholm) was inserted into a right cervical vein and a catheter was inserted into a right femoral artery for measurement of blood pressure and collection of blood.

Plasma exchange (PE)

[0027] The plasma separator (ACH-07S, Asahi Medical, Tokyo) was used for the plasma exchange and the plasma exchange waste liquid purification and circulation dialysis. Anticoagulant (Heparin sodium) was intravenously administered at a dose of 6, 000 units before the extracorporeal circulation, and at a rate of 2, 000 units per hour after the initiation of extracorporeal circulation. A flow rate of blood was set to be 100 ml/min. The plasma exchange was carried by means of a membrane-type plasma separator (OP-05W, Asahi Medical, Tokyo) using a supplementing solution of swine fresh frozen plasma at an amount (L) calculated by the following formula out for 2 hours (10 - 14 ml/min)(Fig.2):

$$\text{body weight (kg)} \times 1/13 \times (1-\text{Ht}/100)$$

Priming of the purifier with plasma exchange waste liquid

[0028] After the completion of the plasma exchange, a filter pump was stopped and a flow path was changed by means of the three-way tap. Then, the purifier was primed with the plasma exchange waste liquid (50 ml/min, 300 ml) by means of a supplementing solution pump (Fig.3).

The plasma exchange waste liquid purification and circulation dialysis (Plasma Recycling Dialysis:PRD)

[0029] After the completion of the priming, the flow path was changed by means of the three-way tap. PRD was carried out for 6 hours using the plasma separator as the dialyzer, which had been used for the plasma separation in PE (Fig.

4). Anion-exchange resin (Plasorba BRS-350, Asahi Medical, Tokyo) was used as the purifier. A flow rate of blood was set to be 100 ml/min and the plasma exchange waste liquid was circulated at a rate of 50 ml/min through an outer space of hollow fiber countercurrently against a blood flow. After the completion, the extracorporeal circulation was stopped and the blood was returned.

Measurement items:

[0030] Artery pressure was continuously measured with the catheter inserted into the femoral artery. Blood was collected before the initiation of PE; at 0. 5, 1, and 2 hours after the initiation of PE; and at 2, 4, 6 (end of PRD) and at 8 hours after the initiation of PRD, and subjected to blood examination with respect to total protein, albumin, Na, Cl, K, urea nitrogen, total bile acid, total bilirubin, Creatinin, LDH, AST, and ALT (n=4). The plasma exchange waste liquid was also colleted at 0.5, 1, and 2 hours after the initiation of PE, followed by determination of a total bile acid and total bilirubin concentration (n=4).

Results:

[0031] It was confirmed that the values of the total bile acid and the total bilirubin were almost the same in the plasma and the plasma exchange waste liquid colleted at 0.5, 1, and 2 hours after the initiation of PE (Fig. 5 & 6). Circulatory dynamics was stable until the end of extracorporeal circulation, and no change in blood pressure (systolic pressure) was observed before and after the transition from PE to PRD (Fig.7). No hemolysis was observed through PE and PRD. The blood examination showed a little increase after the end of the plasma exchange with respect to the numbers of white blood cell (WBC) and red blood cell (RBC), and the values of hemoglobin and hematocrit (Fig.8 - Fig.11). The number of platelet was decreased in PE, but became stable after the transition to PRD (Fig.12). Biochemical examination showed that the values of the total bile acid and the total bilirubin were continuously decreased even after the transition from PE to PRD (Fig.13 & Fig.14). No significant change was observed with respect to the other values through PE and PRD (TABLE 1).

[0032]

[TABLE 1]

	Before PE	End of PE	End of PRD
Total Protein (g/dl)	5.7 ± 0.5	5.0 ± 0.1	5.0 ± 0.3
Albumin (mg/dl)	2.7 ± 0.2	2.4 ± 0.1	2.4 ± 0.2
AST (IU/L)	31 ± 13	36 ± 12	36 ± 8
ALT (IU/L)	18 ± 4	23 ± 3	23 ± 2
LDH (IU/L)	371 ± 51	430 ± 34	435 ± 100
BUN (mg/dl)	6.8 ± 1.9	7.4 ± 1.8	8.8 ± 3.0
Creatinin (mg/dl)	0.8 ± 0.1	0.7 ± 0.1	0.6 ± 0.1
Na (mEq/L)	138 ± 1	138 ± 2	135 ± 2
K (mEq/L)	4.2 ± 0.3	3.6 ± 0.3	3.9 ± 0.5

[Discussion]

[0033] The above examples demonstrated the safety of the combination of PE and PRD, and the possibility of transition or shift from PE to PRD in a short time. In the apparatus according to the present invention, the plasma exchange waste liquid functions as the reservoir and the function of the purifier is supplemented via plasma dialysis. It was also confirmed that such the apparatus of the present invention could effect a sufficient removing efficiency of the harmful substances in the plasma as shown by the changes of the values of the harmful substances in the plasma such as those of the total bilirubin and the total bile acid. Although the anion-exchange resin was used as the purifier in the above examples, it is conceived that any kind of the combination of various adsorbents and hemodialysis may be used as well, and that the purifier may be easily scaled up or exchanged on the way of the therapy. It is also conceived that the apparatus according to the present invention enables a low-invasive and rapid transition from PE to the secondary therapy and is therefore useful as an artificial liver support.

[Industrial Applicability]

[0034] The plasma exchange therapy still has an important place in the therapy of acute liver insufficiency in Japan. The same therapy has a long history and is very safe so that it is considered a therapy that can be performed with little hesitation. This therapy is actually performed in many medical facilities. As the apparatus of the present invention may be very easily composed with a minor modification of the addition of the purifier to the plasma exchange therapy, it is a very useful system that may be easily introduced by doctors skilled in the plasma exchange therapy.

Claims

1. A plasma exchange waste liquid purification and circulation dialysis apparatus wherein at least a portion of separated plasma is purified and circulated as a dialysis solution to dialyze patient's blood to remove harmful substances contained in the plasma.
2. The apparatus of Claim 1, which is used in a simple plasma exchange therapy.
3. The apparatus of Claim 1, which is used in a double-filtration plasma exchange therapy.
4. The apparatus of Claim 1, comprising a purifier and a dialyzer as a constituent element of the apparatus.
5. The apparatus of Claim 4 wherein an apparatus for plasma separation that are used in the plasma exchange functions also as the dialyzer.
6. The apparatus of Claim 4 or 5 wherein the purifier is composed of an adsorption separator.
7. The apparatus of one of Claims 1 to 6 wherein the plasma separated in the plasma exchange therapy functions as reservoir of the dialysis solution.
8. The apparatus of one of Claims 1 to 7, being composed of a hemofilter, a purifier, a three-way tap (A), a pump (4), a line (4) and a line (5) shown in Fig.1.
9. A plasma exchange apparatus incorporating the plasma exchange waste liquid purification and circulation dialysis apparatus according to any one of the preceding claims.
10. The apparatus having the composition shown in Fig. 1.
11. An artificial liver equipped with the apparatus according to any one of the preceding claims.

FIG. 1

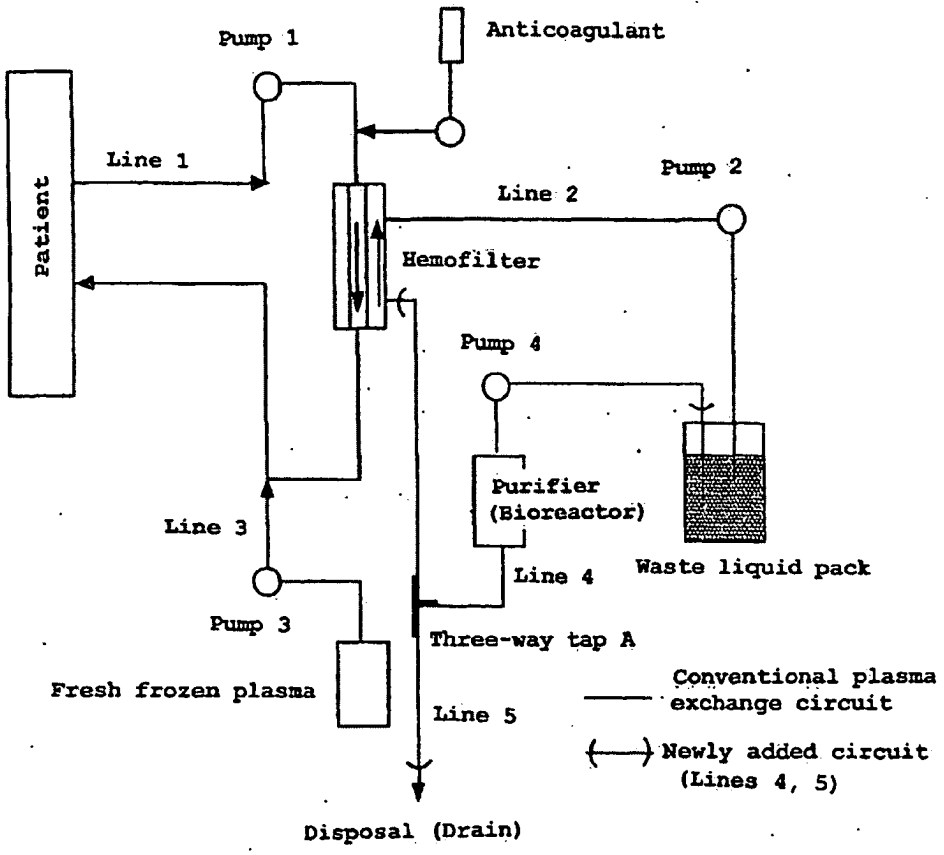

Pump 1
Anticoagulant
Patient
Line 1
Pump 2
Line 2
Hemofilter
Pump 4
Purifier
(Bioreactor)
Line 3
Line 4
Waste liquid pack
Pump 3
Three-way tap A
Fresh frozen plasma
Line 5
Conventional plasma exchange circuit
Newly added circuit (Lines 4, 5)
Disposal (Drain)

FIG. 2

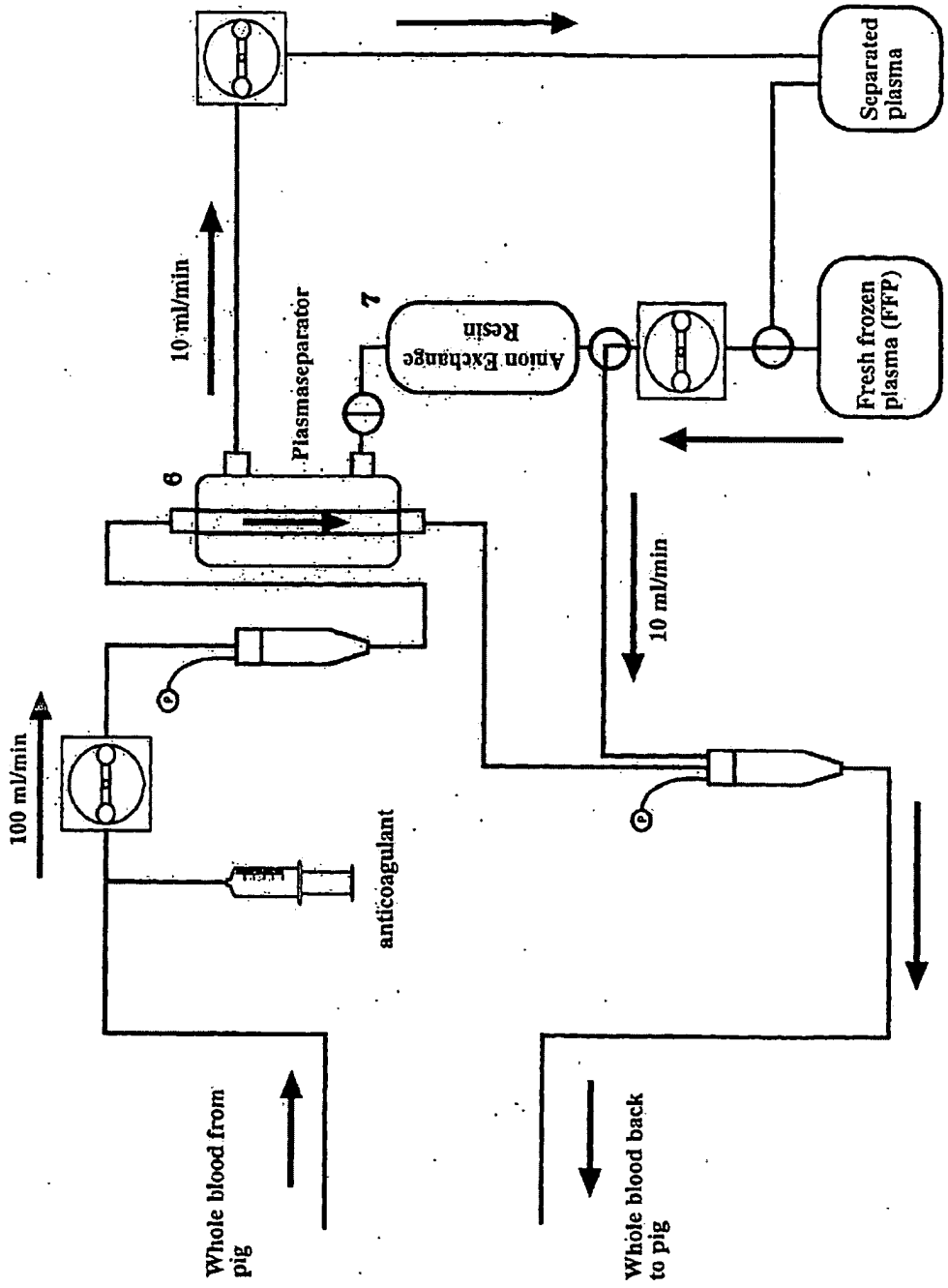

Separated plasma
Fresh frozen plasma (FFP)
Anion Exchange Resin
7
10 ml/min
Plasmaseparator
6
10 ml/min
100 ml/min
anticoagulant
Whole blood from pig
Whole blood back to pig

FIG. 3

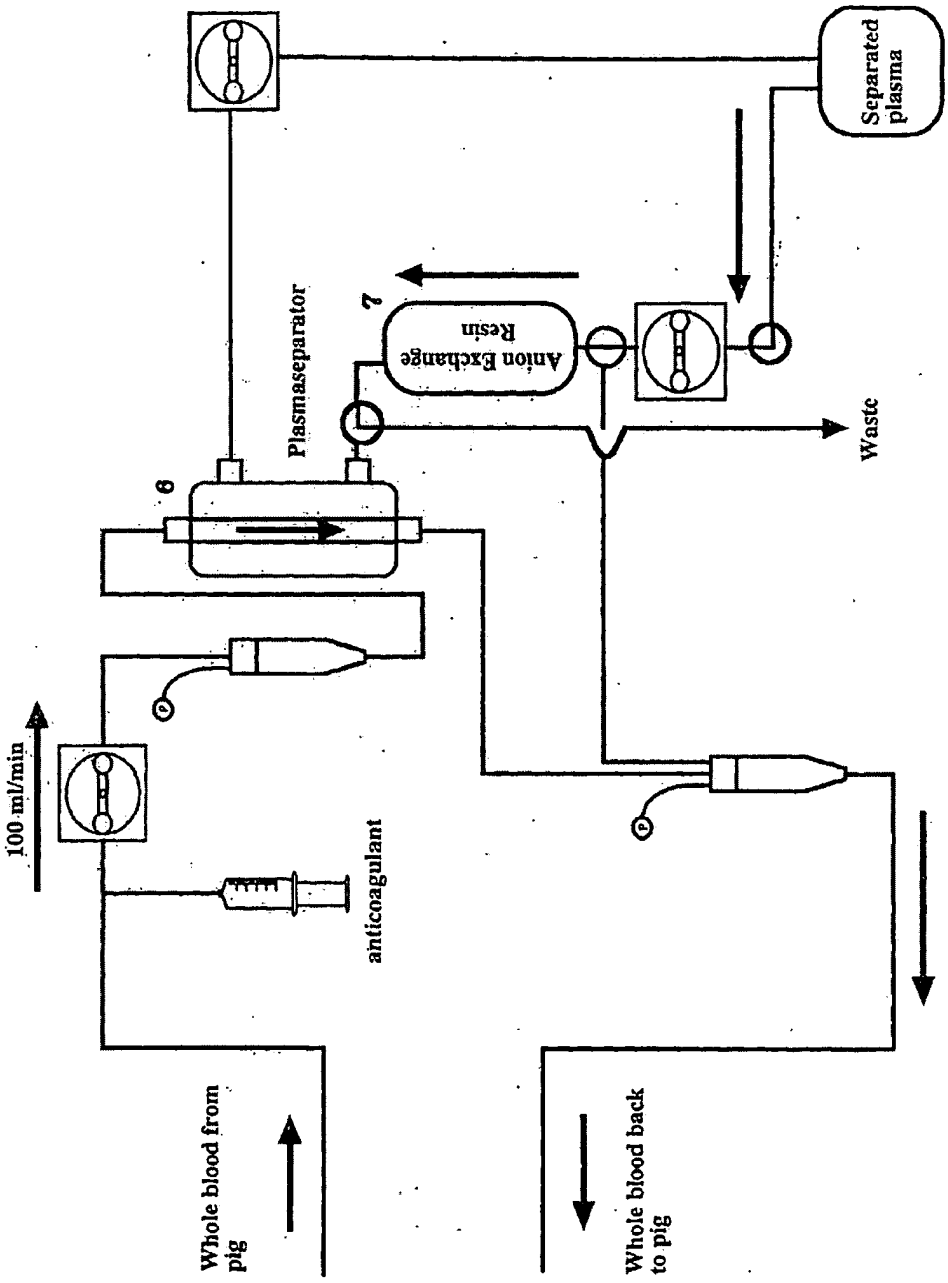

Separated plasma
Anion Exchange Resin
7
Plasmaseparator
Waste
6
100 ml/min
anticoagulant
Whole blood from pig
Whole blood back to pig

FIG. 4

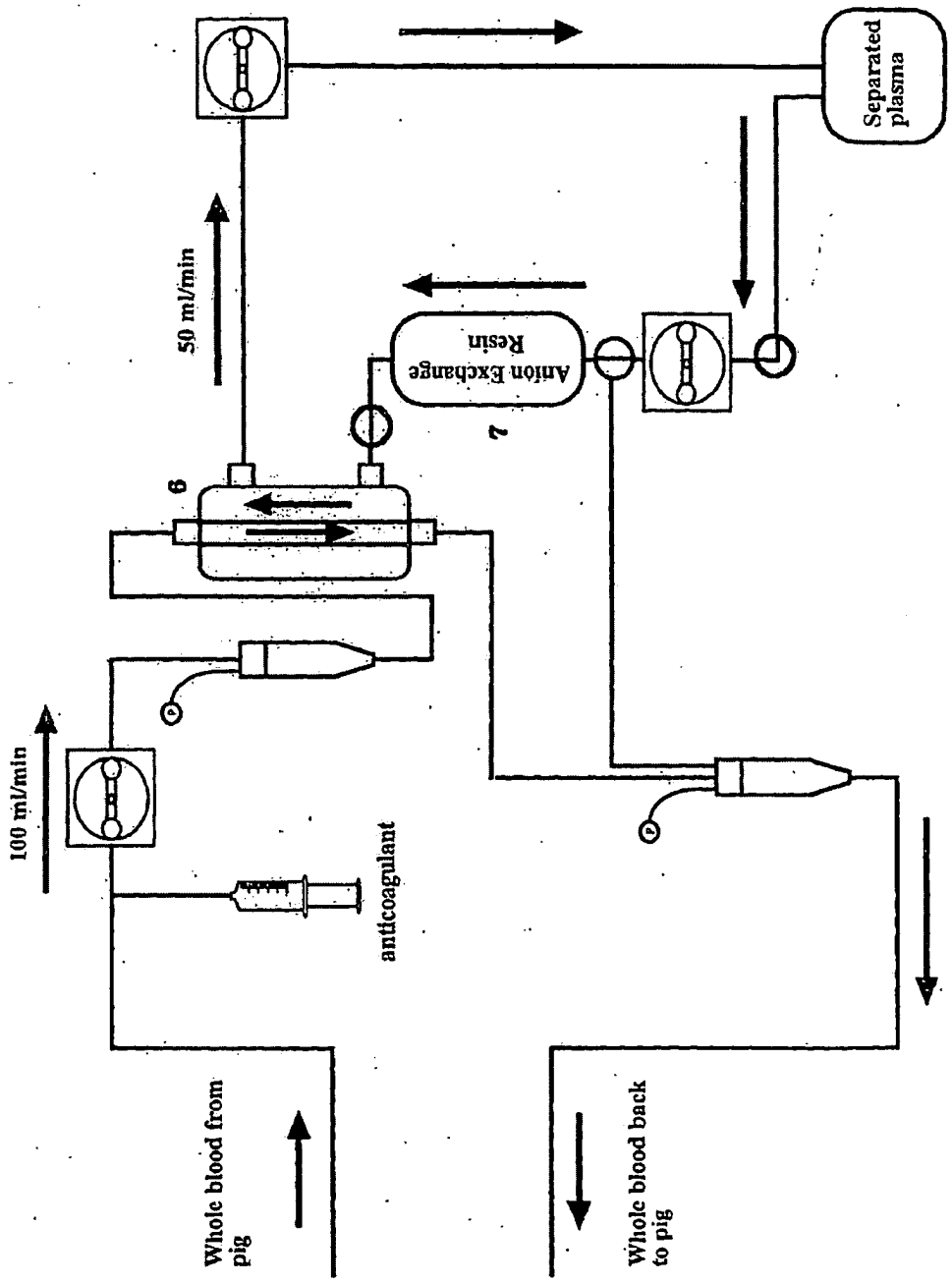

Separated plasma
50 ml/min
Anion Exchange Resin
7
6
100 ml/min
anticoagulant
Whole blood from pig
Whole blood back to pig

FIG. 5

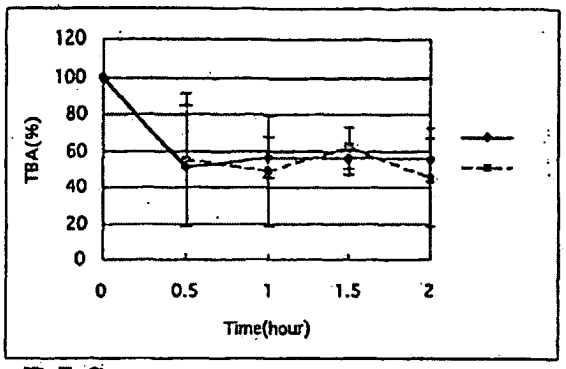


FIG. 6

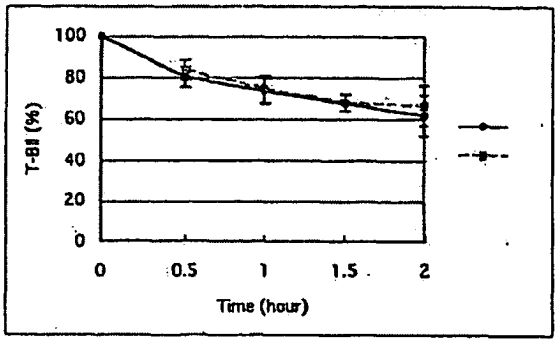


FIG. 7

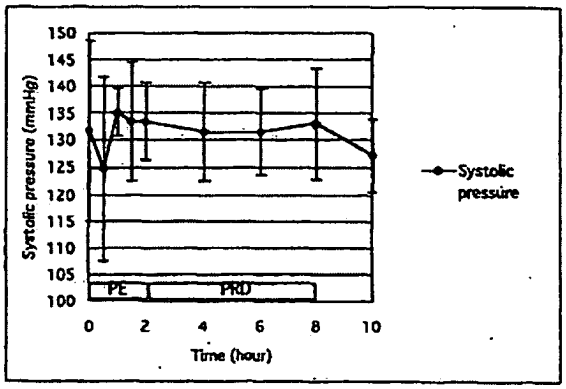


FIG. 8

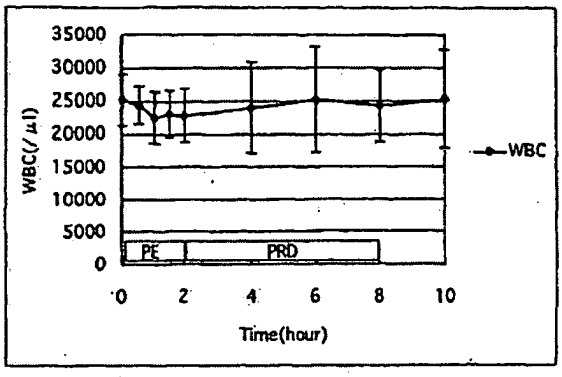


FIG. 9

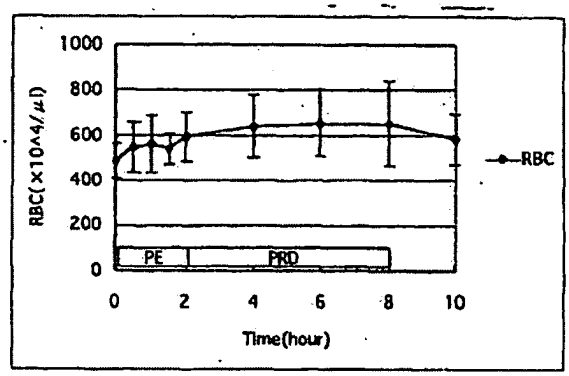


FIG. 10

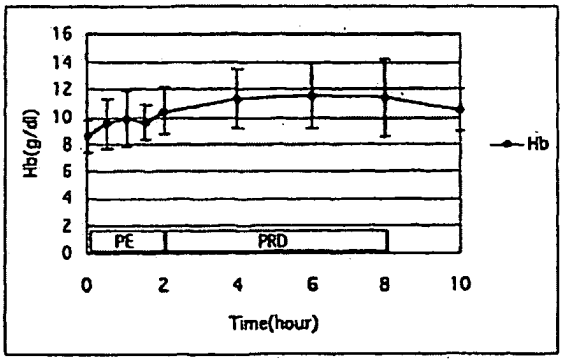


FIG. 11

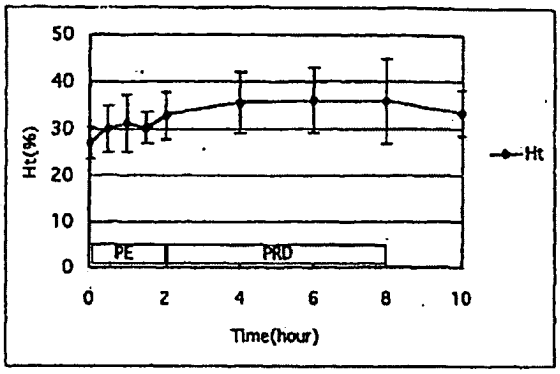


FIG. 12

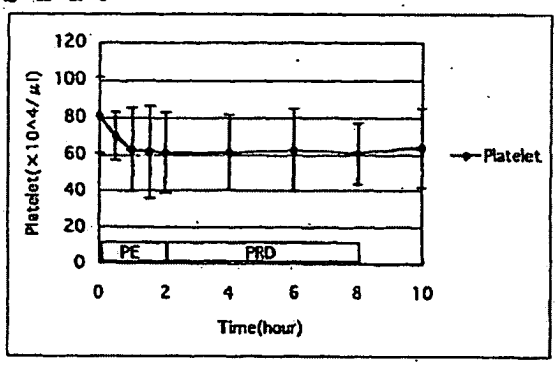


FIG. 13

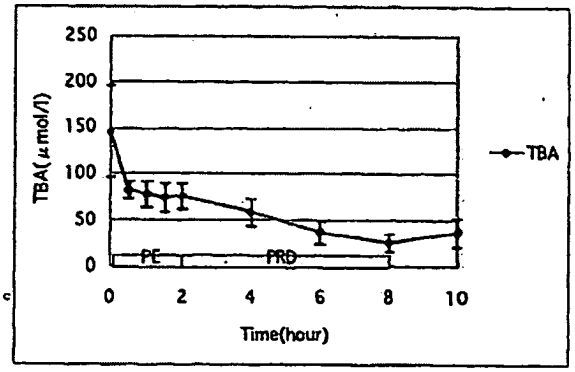
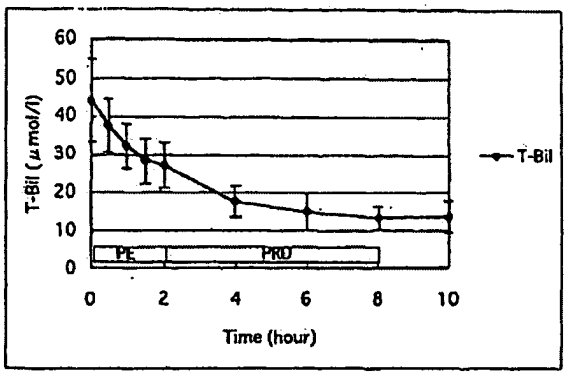


FIG. 14



INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2005/000825

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[7] A61M1/14, 1/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[7] A61M1/02-1/36

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Jitsuyo Shinan Koho	1922-1996	Jitsuyo Shinan Toroku Koho	1996-2005
Kokai Jitsuyo Shinan Koho	1971-2005	Toroku Jitsuyo Shinan Koho	1994-2005

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JP 9-507414 A (HemoCleanse, Inc.), 29 July, 1997 (29.07.97), Full text; all drawings & WO 95/18671 A & US 5536412 A	1-7,9,11
A	JP 7-506765 A (STANGE, Jan), 27 July, 1995 (27.07.95), Full text; all drawings & WO 94/21363 A	1-7,9,11

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search 09 February, 2005 (09.02.05)	Date of mailing of the international search report 01 March, 2005 (01.03.05)
Name and mailing address of the ISA/ Japanese Patent Office Facsimile No.	Authorized officer Telephone No.

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2005/000825

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 8, 10
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
The subject matter of the inventions of claims 8 and 10 cannot be identified because although claims 8 and 10 contain the language "shown in Fig. 1", it is probable that drawings are interpreted in multisense.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest
☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (January 2004)

REFERENCES CITED IN THE DESCRIPTION

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Non-patent literature cited in the description

- **UMEHARA et al.** LIVERAID TM-A Novel Hybrid Bioartificial Liver. *Hepatology*, 2002, vol. 36 (4), 681A [0008]
- **WATANABE et al.** Clinical experience with a bioartificial liver in the treatment of severe liver failure- A pahse I clinical Trial. *Annals of Surgery*, 1997, vol. 225 (5), 484-494 [0008]
- **STANGE et al.** Molecular Adsorbent Recycling System (MARS) : Clinical results of a new membrane based blood purification system for bioartificial liver suppport. *Artif Organs*, 1999, vol. 23 (4), 319-330 [0008]

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(19) 世界知的所有権機関
国際事務局

(43) 国際公開日
2005年8月4日 (04.08.2005)

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(10) 国際公開番号
WO 2005/070478 A1

(51) 国際特許分類[7]: A61M 1/14, 1/34

(21) 国際出願番号: PCT/JP2005/000825

(22) 国際出願日: 2005年1月24日 (24.01.2005)

(25) 国際出願の言語: 日本語

(26) 国際公開の言語: 日本語

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特願2004-311027 2004年10月26日 (26.10.2004) JP

(71) 出願人 (米国を除く全ての指定国について): 独立行政法人科学技術振興機構 (JAPAN SCIENCE AND TECHNOLOGY AGENCY) [JP/JP]; 〒3320012 埼玉県川口市本町四丁目1番8号 Saitama (JP).

(72) 発明者; および

(75) 発明者/出願人 (米国についてのみ): 梅原 豊 (UMEHARA, Yutaka) [JP/JP]; 〒0368183 青森県弘前市品川町120-1-302 Aomori (JP). 梅原 実 (UMEHARA, Minoru) [JP/JP]; 〒0380004 青森県青森市宮田1-10-10 Aomori (JP). 佐々木 睦男 (Sasaki mutsuo) [JP/JP]; 〒0368227 青森県弘前市桔梗野2-16-22 Aomori (JP).

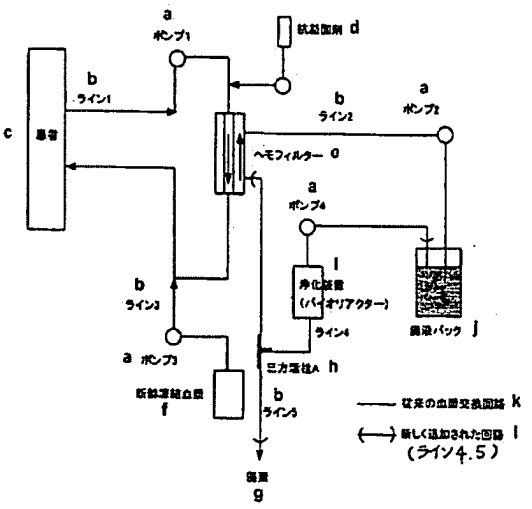
(74) 代理人: 阿部 正博 (ABE, Masahiro); 〒2740825 千葉県船橋市前原西二丁目14番1号ダイアパレス津田沼1001号 Chiba (JP).

(81) 指定国 (表示のない限り、全ての種類の国内保護が可能): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,

[続葉有]

(54) Title: PLASMA EXCHANGE WASTE LIQUID PURIFICATION CIRCULATION DIALYZER

(54) 発明の名称: 血漿交換廃液浄化循環透析装置



a PUMP
b LINE
c PATIENT
d ANTICOAGULANT
e HEMOFILTER
f FRESH FROZEN PLASMA
g DRAIN
h THREE-WAY TAP A
i PURIFYER (BIOREACTOR)
j WASTE LIQUID PACK
k CONVENTIONAL PLASMA EXCHANGE CIRCUIT
l NEWLY ADDED CIRCUIT (LINES 4, 5)

(57) Abstract: An apparatus in which in plasma exchange therapy, valuable plasma is recycled as a dialysis solution without disposing of the same, which apparatus is operable with only some modifications applied to the conventional plasma exchange equipment. There is provided a unit for use in plasma exchange therapy characterized in that at least portion of separated plasma is purified, circulated as a dialysis solution and used to dialyze patient's blood, thereby removing hazardous substances contained in the plasma. There are further provided a plasma exchange apparatus including the above unit and an artificial liver equipped with the apparatus.

(57) 要約: 本発明は、血漿交換療法において、貴重な血漿を廃棄せずに透析液として再利用し、且つ、従来の血漿交換装置に若干の修飾を加えるのみで実施することが可能な装置を提供することを目的とする。 本発明は、血漿交換療法に使用する装置であって、分離された血漿の少なくとも一部を浄化した後、透析液として循環させて患者血液を透析し血漿中に含まれる有害物を除去することを特徴とする、該装置。該装置が組み込まれた血漿交換装置、及び該装置を備えた人工肝臓に関する。

WO 2005/070478 A1

LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) 指定国 (表示のない限り、全ての種類の広域保護が可能): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), ユーラシア (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), ヨーロッパ (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

添付公開書類:
— 国際調査報告書

2文字コード及び他の略語については、定期発行される各PCTガゼットの巻頭に掲載されている「コードと略語のガイダンスノート」を参照。

明 細 書

血漿交換廃液浄化循環透析装置

技術分野

[0001] 本発明は、患者血液から分離された血漿の一部を浄化し、それを透析液として使用して血漿透析を行うことを特徴とする、血漿交換廃液浄化循環透析装置に関する。

背景技術

[0002] 血漿交換療法(血漿分離交換法)は、患者血漿を正常者より得られた新鮮凍結血漿などで置き換える療法であり、異常抗体や免疫複合体、又は正常な因子であるが過剰に生産されることが原因となる疾患において、他の治療法が効果を奏さないか不十分なときに行われる。対象疾患としては急性肝不全、グッドパスチャー症候群に代表される抗糸球体基底膜抗体病、重筋無力症、ギラン・バレー症候群、壊死性血管炎、血栓性血小板減少性紫斑病、家族性コレステロール血症がある。

[0003] このような血漿交換療法として、従来行われている代表的な方法として以下のものを挙げることが出来る。

[0004] [単純血漿交換療法]

生体においては始めに血漿成分をすべて除去した後に新しい血漿を注入すること(正しい意味での「交換」)は生体の機能維持の点で不可能である。このため、ヘモフィルター(血液フィルター)あるいは血漿分離器における遠心力などにより血球と血漿を分離し、分離された患者血漿を廃棄しながら同時に新鮮凍結血漿を注入する方法である。しかし、この方法では患者血漿は常に体内で注入された新鮮血漿と撹拌された後に分離、廃棄されることになるため、ある一定量の血漿交換終了時の患者血漿の組成と廃棄された血漿の組成はほぼ同一であることが推察される。すなわち、「血漿交換療法」とは言うものの、実際は一定量の新鮮血漿で患者血漿を希釈し、余剰分を廃棄していることに他ならない。

[0005] [二重濾過血漿交換療法]

単純血漿交換療法に比しより選択的に血漿蛋白を除去し、一部の血漿を返し、補

充液としてアルブミン溶液を用いる方法であるが、分子量分画による分離のため、必要蛋白も除去される可能性がある。

[0006] 更に、血漿中の病因物質及び毒性物質を除去するための代表的な方法としては、以下の血漿吸着療法及びMARSを挙げることができる。

[0007] [血漿吸着療法]

使用する吸着材の殆どが血液凝固、血小板減少、溶血の観点から血漿での灌流を必要とするため、血球と血漿を分離した後、分離された血漿を吸着剤と接触させることによって、血漿中に含まれている病因物質を選択的に除去する方法である。また病態(急性肝不全等)によっては単純血漿交換療法と併施する必要が生じる場合もあり、装置の複雑化、手技の煩雑化の観点からより簡便に他療法と組み合わせる方法が必要とされる。

[0008] [Molecular Adsorbent Recycling System(MARS(登録商標))]

急性肝不全において透析液としてアルブミン溶液を用い、蛋白結合性の毒性物質のみを選択的に除去する目的に開発された装置である。現在ドイツ、フランスを中心に他施設無作為抽出試験が行われている。しかし、除去効率が透析膜に依存する部分が大きく(アルブミンは透過せず、アルブミンに結合した毒性物質のみを透過する)また、その概念に対しての異論もあり、新しい技術として確立されるには時間を要するものと考えられる。

非特許文献1:Umehara, et al., LIVERAID TM-A Novel Hybrid Bioartificial Liver- Hepatology 2002, 36(4) suppl.:681A

非特許文献2:Watanbe et al., Clinical experience with a bioartificial liver in the treatment of severe liver failure-A phase I clinical trial- Annals of Surgery 1997: 225(5):484-494

非特許文献3:Stange, et al., Molecular Adsorbent Recycling System (MARS): Clinical results of a new membrane based blood purification system for bioartificial liver support, Artif Organs 1999: 23(4):319-330

発明の開示

発明が解決しようとする課題

[0009] 現在日本においては、新鮮凍結血漿はすべてボランティアからの献血によりまかなわれており、従って、血漿交換療法においても、このような貴重な生体由来の資源をさらに有効に活用する方法が求められている。

[0010] そこで、本発明者は、このような従来技術における問題点上記課題を解決することを目的として研究を重ねた結果、血漿交換廃液を二次的な治療法に応用すること、より具体的には、血漿交換廃液を浄化し透析液として用いる方法を見出し、本発明を完成した。

課題を解決するための手段

[0011] 即ち、本発明は、分離された血漿(Separated plasma:血漿交換廃液)の少なくとも一部を浄化した後、透析液として循環させて患者血液を透析し血漿中に含まれる有害物を除去することを特徴とする、血漿交換廃液浄化循環透析装置に係る。既に記載したように、血漿交換療法の代表的な例としては、単純血漿交換療法及び二重濾過血漿交換療法を挙げることが出来るが、本発明装置はこれら方法に限定されず、広く血漿交換療法一般に使用することが出来るものである。

[0012] 上記の本発明装置の一具体例では、浄化装置及び透析器が構成要素として含まれる。この透析器における循環される分離血漿による患者血液の透析は、当業者に公知の任意の手段・方法で行うことが出来る。かかる透析器(透析装置)は、血漿交換に使用する血漿分離器(プラズマセパレーター:Plasma separator)又はヘモフィルターのような血漿分離装置とは別に設けることも出来るし、或いは、より簡便には、このような血漿分離装置を透析器としても機能させることも可能である。

[0013] 浄化装置(バイオリアクター)において、分離された血漿の浄化は当業者に公知の任意の手段・方法で行うことが出来る。このような装置において、分離された血漿中の各種有害物質(病因物質、毒性物質)が血漿中から除去される。例えば、浄化装置が吸着分離装置から構成されるような場合には、該装置に装備された、各種イオン交換樹脂、ジビニルベンゼン、ジビニルトルエン、スチレン等から合成された各種多孔性共重合体、活性炭、及び、アルミナなどの任意の吸着剤の作用によって、血漿蛋白質に吸着していた各種有害物質が吸着剤に吸着することによって血漿中から除去される。

[0014] 更に、本発明装置の好適例では、分離された血漿が透析液のリザーバーとして機能するような構成とすることが出来る。本発明装置には、その他、ポンプ、ライン、三方活栓等の当業者に公知の要素を含むことが出来る。本発明装置の一具体例として、図1に示される、ヘモフィルター、浄化装置、三方活栓A、ポンプ4、ライン4、ライン5から構成される装置を挙げることが出来る。

[0015] 本発明の血漿交換廃液浄化循環透析装置は、当該技術分野で使用されている任意のタイプの血漿交換装置に簡単に付加して、一部として使用することが出来る。従って、本発明は、本発明の血漿交換廃液浄化循環透析装置が組み込まれた、血漿交換装置にも係る。

[0016] 現在、急性肝不全に対する治療または肝移植までの橋渡しとして肝細胞または肝組織を用いた人工肝臓の開発が進められている。このうち多くのものは血漿を分離し酸素化、バイオリアクターに誘導した後に血球成分と混和し患者体内に戻すシステムを採用している。急性肝不全患者血漿中には用いられた肝細胞または肝組織の機能を低下させる成分が含まれていることが報告されており、バイオリアクターを用いた治療の前に血漿交換療法により有害物質の濃度を下げ、その後に細胞または組織を用いた治療を行うことは非常に有効であると考えられる。

[0017] 従って、本発明は以上の本発明の血漿交換廃液浄化循環透析装置を備えた人工肝臓(ハイブリッド型を含む)にも係るものである。このような人工肝臓は、上記の人工肝臓開発において、種々のタイプのバイオリアクターのプラットフォームとなり得るものと考えられる。

発明の効果

[0018] 本発明の装置を使用することにより、貴重な血漿を廃棄せずに透析液として再利用することにより、血漿中に含まれる有害物を効率的に除去することができる。更に、本発明装置は従来の血漿交換装置に若干の修飾を加えるのみで実施することが可能であるので、単純血漿交換療法終了後に直ちに血漿吸着療法等の他の療法に移行することができる。また、血液浄化療法施行時には装置のプライミングボリュームがしばしば問題になるが、この装置では血漿交換廃液をリザーバー、プライミング液として用いることができるため、循環動態の不安定な患者、小児等の体の小さい患者に対

しても安全に施行可能である。

図面の簡単な説明

[0019] [図1]本発明装置の一具体例を示す。

[図2]実施例における血漿交換時の回路を示す。

[図3]実施例における浄化装置の血漿交換排液によるプライミング時の回路を示す。

[図4]実施例における血漿交換排液浄化循環透析時の回路を示す。

[図5]PE開始0.5、1、2 時間後の血漿中および血漿交換排液中の総胆汁酸(TBA)値の変化を示すグラフである。PE前の血漿中の値を100として以後の値を%で表示した。

[図6]PE開始0.5、1、2 時間後の血漿中および血漿交換排液中の総ビリルビン(T-Bil)値の変化を示すグラフである。PE前の血漿中の値を100として以後の値を%で表示した。

[図7]PE からPRD への移行前後で血圧(収縮期圧:Systolic pressure)の推移を示すグラフである。

[図8]PE及びPRD を通しての白血球(WBC)数の推移を示すグラフである。

[図9]PE及びPRD を通しての赤血球(RBC)数の推移を示すグラフである。

[図10]PE及びPRD を通してのヘモグロビン(Hb)値の推移を示すグラフである。

[図11]PE及びPRD を通してのヘマトクリット(Ht)値の推移を示すグラフである。

[図12]PE及びPRD を通しての血小板(Platelet)数の推移を示すグラフである。

[図13]PE及びPRD を通しての総胆汁酸(TBA)値の推移を示すグラフである。

[図14]PE及びPRD を通しての総ビリルビン(T-Bil)値の推移を示すグラフである。

符号の説明

[0020] 1:ポンプ、ライン

2:ポンプ、ライン

3:ポンプ、ライン

4:ポンプ、ライン

5:ライン

6:血漿分離器(Plasmaseparator)

7:浄化装置(アニオン交換樹脂)

発明を実施するための最良の形態

[0021] 以下、図1に則して、本発明の一具体例を説明する。各番号は図1中に示した番号と一致する。尚、当業者であれば、当該技術分野における技術常識及び本明細書の記載に基づき、本発明の技術的特徴を有するその他の各種態様を容易に想到することが可能であり、それらの各種態様も本発明の技術的範囲に属することは明白である。

[0022] はじめに患者血液はライン1よりポンプ1を用いてヘモフィルター(透析器としても機能する)に導入される(100 ml/min)。ポンプ2により血漿が分離され、この血漿交換廃液が廃液バックへ送られる(5-10 ml/min)。同時に患者にはライン3より新鮮凍結血漿(Fresh frozen plasma: FFP)をポンプ3を用い同速で注入する。この間はポンプ4は停止している。ライン4、5は三方活栓Aにより閉鎖されている。定められた量の血漿交換が終了後、ポンプ2、3を停止、三方活栓Aでライン4、5を開放した後ポンプ4用い廃液バック中の血漿交換廃液を定められた量ライン5より廃棄する(たとえば2リットルの血漿交換をした場合、1リットルを廃棄し、残りの1リットルを廃液バック中に残す(ライン4および浄化装置の血漿交換廃液によるプライミング)。三方活栓Aにてライン5を閉鎖する。ポンプ2および4を同速度で回転(例えば400 ml/min)し、血漿交換廃液の浄化および血漿透析を行う。

[0023] 上記装置に使用される、血漿分離装置(ヘモフィルター、又はプラズマセパレーター)、ポンプ、ライン等の各構成要素は当業者に公知の任意のものを使用することが出来る。また当業者であれば本明細書の記載に基づいて図1に示された装置を容易に使用することができる。

実施例

[0024] 次に、実際にブタ高ビリルビン血漿モデルを用いた動物実験により、本発明の装置を用いる血漿交換及び血漿交換廃液浄化循環透析の具体例を示す。尚、以下の実施例は本発明の技術的範囲を何等限定するものではない。

[0025] 方法:

[実験動物]

雌性肥育ブタ(体重25ー30 kg)を金属飼育ケージにて飼育し実験に用いた。飼育動物は日照8ー20 時、恒温恒湿(22±2℃、55±10%)とし、水道水を自由摂取とした。実験はすべて「弘前大学動物実験に関する指針」に従って行われた。すべての手術および体外循環は以下の方法による全身麻酔下に行われた。実験動物は前日夜より絶食、水のみ自由摂取とし、麻酔の導入はケタミン(15 mg/kg)及びアトロピン(0.01 mg/kg)の筋肉内注射により行われた。入眠後耳介静脈より血管確保し、チオペンタールナトリウム100mg を投与後気管内挿管を行った。麻酔の維持はベンチレーターによる人工呼吸下にミダゾラム(0.3 mg/kg/h)、ペンタゾシン(0.3mg/kg/h)、パンクロニウムブロミド(0.04 mg/kg/h)にて行った。

[0026] [ブタ高ビリルビン血漿モデル]

全身麻酔下に上腹部正中で開腹し、胆嚢摘出、総胆管結紮切離により作製した。術後は飼育ケージにて経過観察を行った。7日後再度全身麻酔を行い、右内頸静脈に体外循環用ダブルルーメンカテーテル(GamCath, Gambro, Stockholm)、右大腿動脈に血圧測定および採血用カテーテルを挿入した。

[0027] [血漿交換(Plasma Exchange, PE)]

血漿交換および血漿交換排液浄化循環透析には血液濾過装置(Plasma separator: ACH-07S, Asahi Medical, Tokyo)を用いた。抗凝固剤はヘパリンナトリウムを体外循環開始前に6000 単位静注、開始後は2000 単位/時間で投与した。血流量は100 ml/分とし、血漿交換は膜型血漿分離器(OP-05W, Asahi Medical, Tokyo)を用い補充液にブタ新鮮凍結血漿を用いて体重(kg) x 1/13 x (1- Ht/100)で算出された量(リットル)を2時間で施行した(10-14ml/分) (図2)。

[0028] [浄化装置の血漿交換排液によるプライミング]

血漿交換終了後、濾過ポンプを停止し三方活栓を用いて流路変更を行った。その後補充液ポンプを用い血漿交換排液 (50 ml/分, 300 ml)による浄化装置のプライミングを行った(図3)。

[0029] [血漿交換排液浄化循環透析 (Plasma Recycling Dialysis, PRD)]

プライミング終了後、三方活栓を用いて流路変更を行い、PE 時に血漿分離に用いていたプラズマセパレーターを透析器として用いることによるPRD を6 時間施行した(

図4)。浄化装置にはアニオン交換樹脂 (Plasorba BRS- 350, Asahi Medical, Tokyo) を用いた。血流量は100 ml/分とし、血流に対向で血漿交換排液を50 ml/分で中空糸外腔を循環させた。終了後体外循環を停止し返血を施行した。

[0030] 測定項目:

大腿動脈に挿入されたカテーテルより動脈圧測定を持続的に行った。採血はPE前、PE開始0.5、1、2 時間後、PRD 開始2、4、6(PRD 終了時)、8 時間後に行い、血液検査、総蛋白、アルブミン、ナトリウム、クロール、カリウム、尿素窒素、総胆汁酸、総ビリルビン、クレアチニン、LDH, AST, ALT について測定した (n=4)。また血漿交換排液をPE 開始0.5、1、2 時間後に採取し、総胆汁酸、総ビリルビン濃度の測定を行った(n=4)。

[0031] 結果:

PE開始0.5、1、2 時間後の血漿中および血漿交換排液中の総胆汁酸(TBA)値、及び総ビリルビン(T-Bil)値の比較では、血漿中と血漿交換排液中の値がほぼ同一であることが実験的に確認された(図5、図6)。循環動態は体外循環終了時まで安定しており、PE からPRD への移行前後で血圧(収縮期圧)変化を認めなかった(図7)。PE及びPRD を通して溶血は認めなかった。血液検査では白血球数、赤血球数、ヘモグロビン値、ヘマトクリット値に血漿交換終了後軽度の上昇を認めた(図8ー図11)。血小板数はPE で低下を認めたがPRD 移行後は安定していた(図12)。生化学検査では総胆汁酸値、総ビリルビン値がPE からPRD 移行後も持続的に低下した(図13、図14)。その他の値についてはPE からPRD を通して大きな変化を認めなかった(表1)。

[0032] [表1]

	PE 前	PE 終了時	PRD 終了時
Total Protein (g/dl)	5.7 ± 0.5	5.0 ± 0.1	5.0 ± 0.3
Albumin (mg/dl)	2.7 ± 0.2	2.4 ± 0.1	2.4 ± 0.2
AST (IU/L)	31 ± 13	36 ± 12	36 ± 8
ALT (IU/L)	18 ± 4	23 ± 3	23 ± 2
LDH (IU/L)	371 ± 51	430 ± 34	435 ± 100
BUN (mg/dl)	6.8 ± 1.9	7.4 ± 1.8	8.8 ± 3.0
Creatinin (mg/dl)	0.8 ± 0.1	0.7 ± 0.1	0.6 ± 0.1
Na (mEq/L)	138 ± 1	138 ± 2	135 ± 2
K (mEq/L)	4.2 ± 0.3	3.6 ± 0.3	3.9 ± 0.5

[0033] 考察:

今回の検討でPE+PRD の安全性が示され、またPE から短時間でPRD に移行可能であることが示された。本発明装置を用いた本法は血漿交換排液をリザーバーとし血漿透析を介して浄化装置の機能を付加する方法であるが、血漿中の有害物である総胆汁酸及び総ビリルビン値の推移から十分な除去効率が得られることが確認された。今回の検討では浄化装置にアニオン交換樹脂のみを用いたが、本発明においては浄化装置のスケールアップは容易であり、種々の吸着剤や血液透析(Hemodialysis)を組み合わせて施行することや治療途中で浄化装置を交換することも可能であると考えられた。PE から低侵襲かつ速やかに二次的治療に移行を可能にするものであり人工肝臓サポート(artificial liver support)として有用であると考えられた。

産業上の利用可能性

[0034] 国内における急性肝不全の治療においては血漿交換療法は依然として重要な位置を占めている。同治療は歴史が長く、安全性が高く、比較的躊躇せずに施行される治療法の一つであろうと考えられ、実際に多くの施設において施行されている。本発明装置は、この血漿交換療法において軽微に修飾する形でバイオリアクターを付加することによって簡便に構成することができ、血漿交換に習熟した医師にとっては非常に導入しやすいシステムとして有用である。

請求の範囲

[1] 分離された血漿の少なくとも一部を浄化した後、透析液として循環させて患者血液を透析し血漿中に含まれる有害物を除去することを特徴とする、血漿交換廃液浄化循環透析装置。

[2] 単純血漿交換療法で使用する、請求項1記載の装置。

[3] 二重濾過血漿交換療法で使用する、請求項1記載の装置。

[4] 浄化装置及び透析器を構成要素として含む、請求項1ー3のいずれか一項に記載の装置。

[5] 血漿交換に使用する血漿分離装置が透析器としても機能する、請求項4に記載の装置。

[6] 浄化装置が吸着分離装置から構成される、請求項4又は5記載の装置。

[7] 血漿交換療法において分離された血漿が透析液のリザーバーとして機能する、請求項1ー6のいずれか一項に記載の装置。

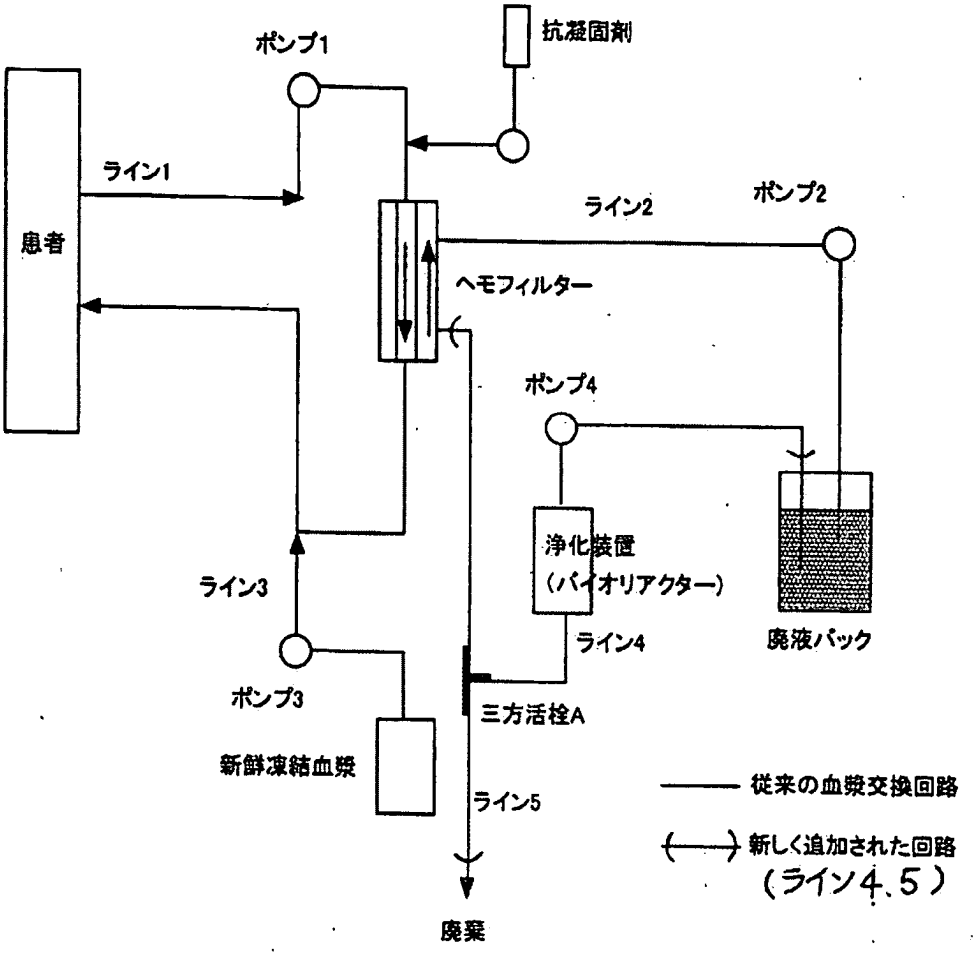
[8] 図1に示される、ヘモフィルター、浄化装置、三方活栓A、ポンプ4、ライン4、ライン5から構成される、請求項1ー7のいずれか一項に記載の装置。

[9] 前記請求項のいずれか一項に記載の血漿交換廃液浄化循環透析装置が組み込まれた、血漿交換装置。

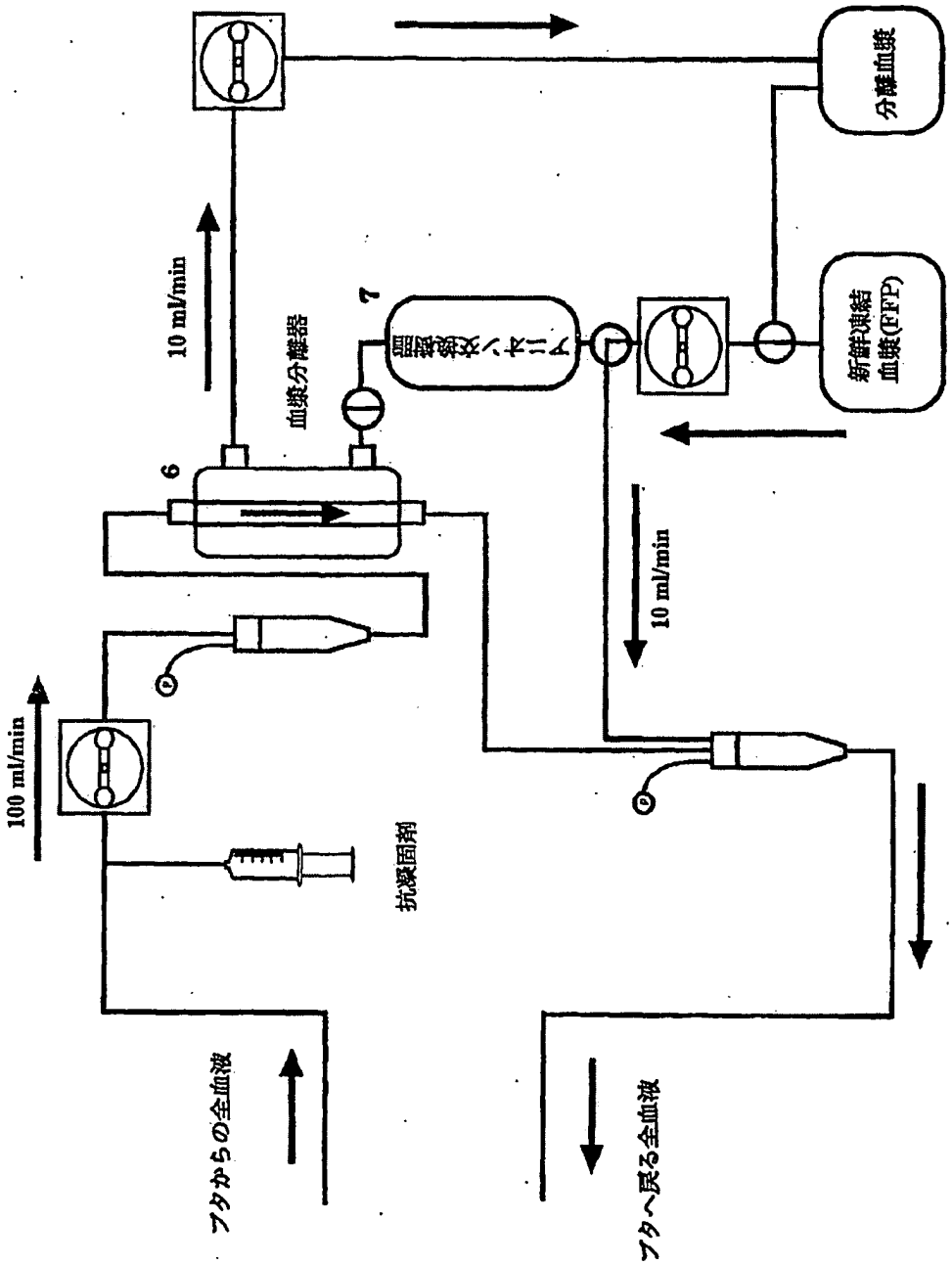
[10] 図1に示される構成から成る、請求項9記載の装置。

[11] 前記請求項のいずれか一項に記載の装置を備えた人工肝臓。

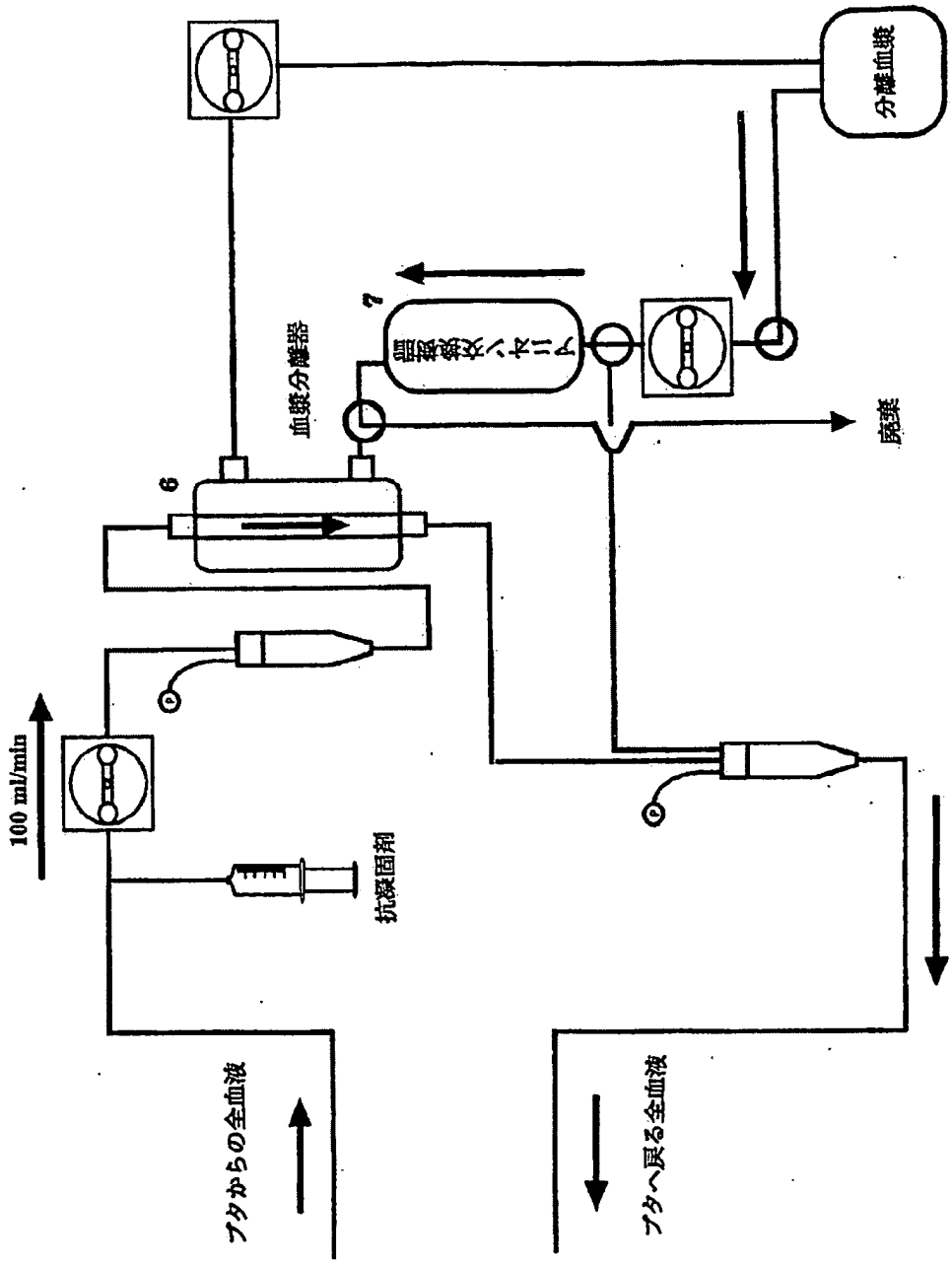
[図1]


ポンプ1
抗凝固剤
ライン1
患者
ライン2
ポンプ2
ヘモフィルター
ポンプ4
浄化装置
(バイオリアクター)
廃液パック
ライン3
ライン4
ポンプ3
三方活栓A
新鮮凍結血漿
ライン5
廃棄
従来の血漿交換回路
新しく追加された回路
(ライン4.5)

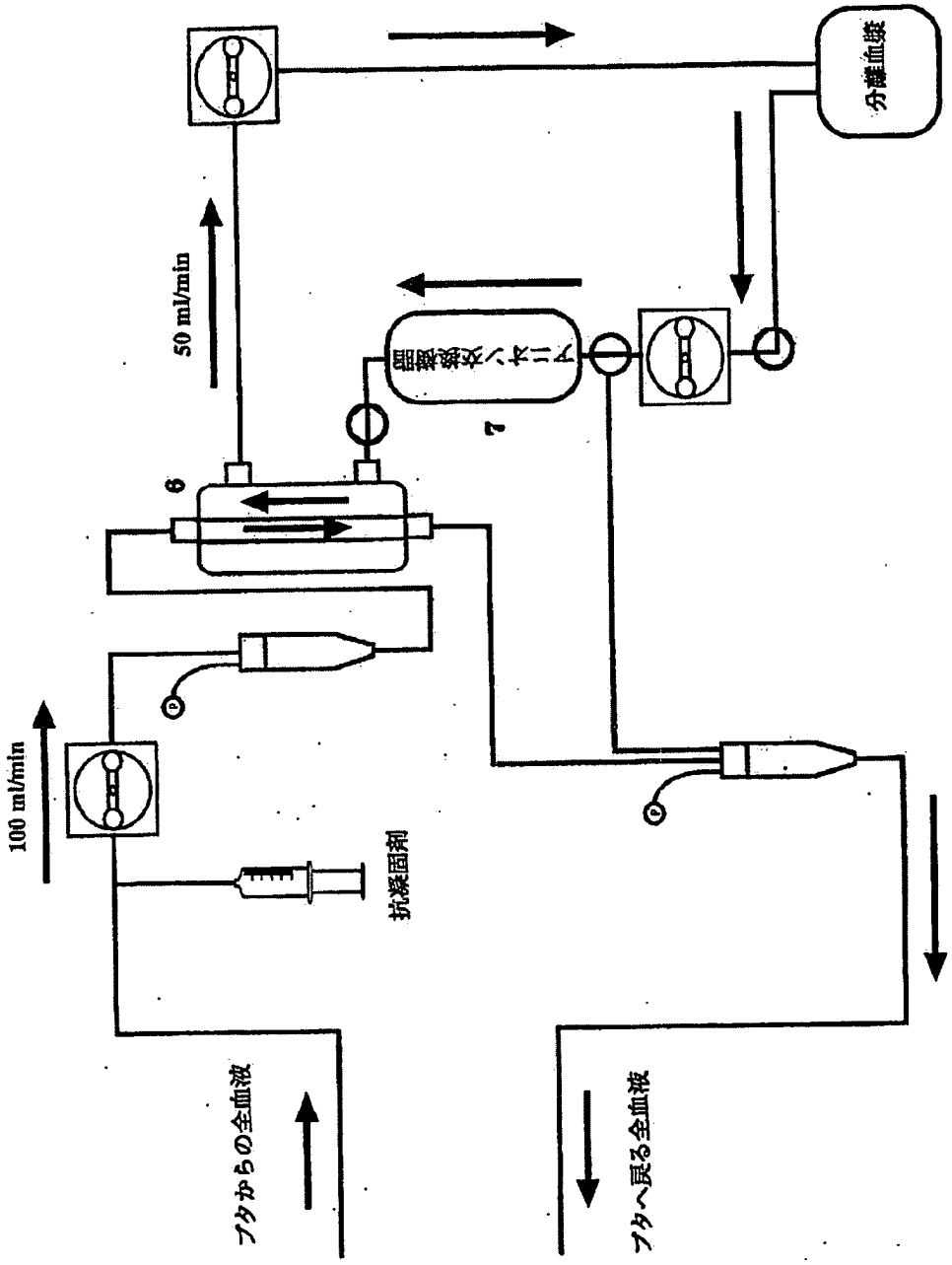
[図2]


分離血漿
新鮮凍結血漿(FFP)
10 ml/min
血漿分離器
7
6
10 ml/min
100 ml/min
抗凝固剤
ブタからの全血液
ブタへ戻る全血液

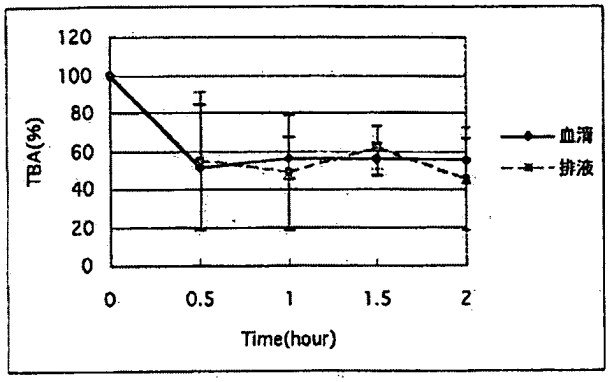
[図3]


分離血漿
7
ファットフィルター
血漿分離器
廃棄
6
100 ml/min
抗凝固剤
ブタからの全血液
ブタへ戻る全血液

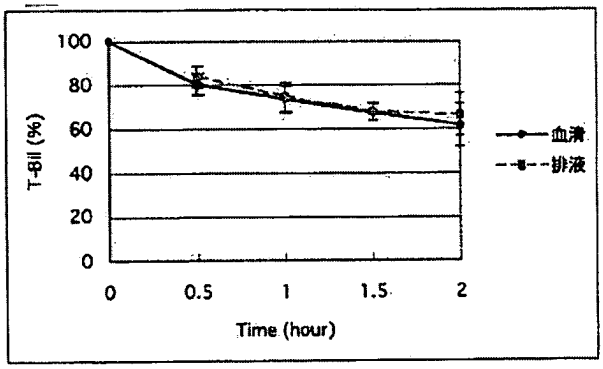
[図4]


分離血漿
50 ml/min
ファンオン交換樹脂
7
6
100 ml/min
抗凝固剤
ブタからの全血液
ブタへ戻る全血液

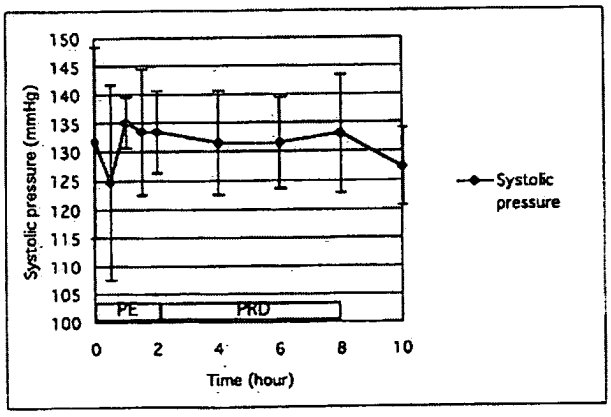
[図5]


120
100
80
60
40
20
0
TBA(%)
0
0.5
1
1.5
2
Time(hour)
血清
排液

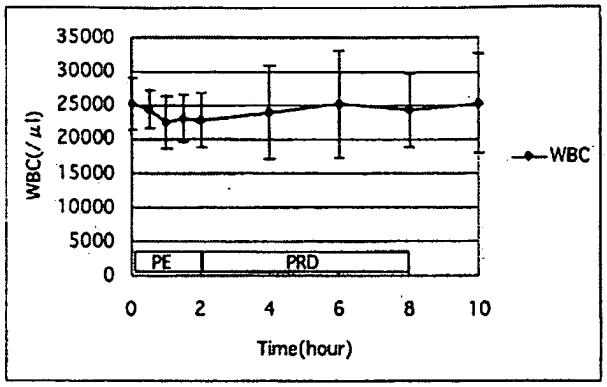
[図6]


100
80
60
40
20
0
T-Bil (%)
0
0.5
1
1.5
2
Time (hour)
血清
排液

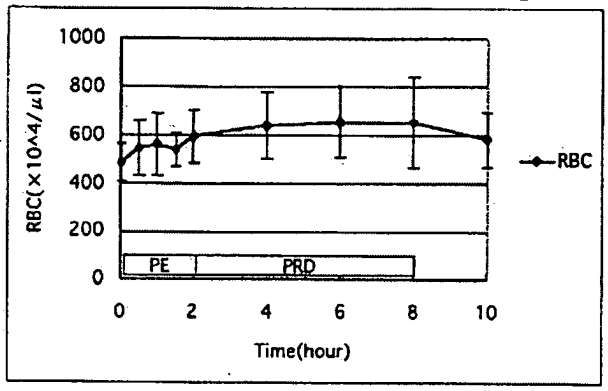
[図7]


150
145
140
135
130
125
120
115
110
105
100
Systolic pressure (mmHg)
PE
PRD
0
2
4
6
8
10
Time (hour)
Systolic pressure

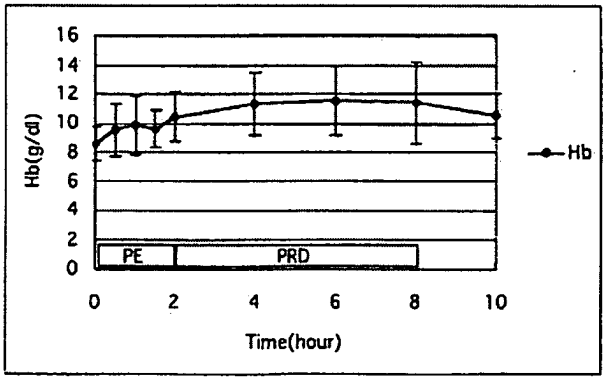
[図8]


35000
30000
25000
20000
15000
10000
5000
0
WBC(/μl)
PE
PRD
0
2
4
6
8
10
Time(hour)
WBC

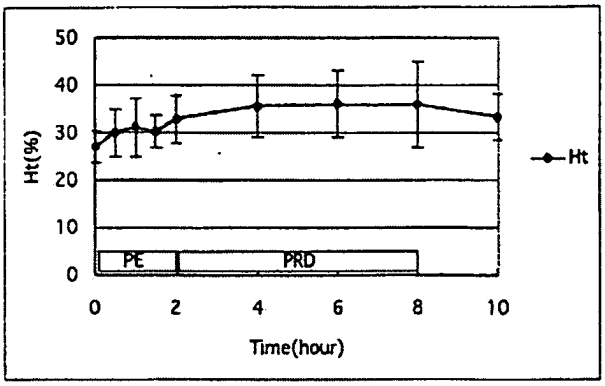
[図9]


1000
800
600
400
200
0
RBC(×10^4/μl)
PE
PRD
0
2
4
6
8
10
Time(hour)
RBC

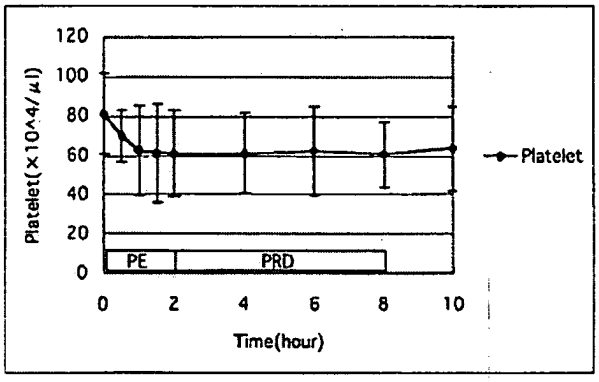
[図10]


16
14
12
10
8
6
4
2
0
Hb(g/dl)
PE
PRD
0
2
4
6
8
10
Time(hour)
Hb

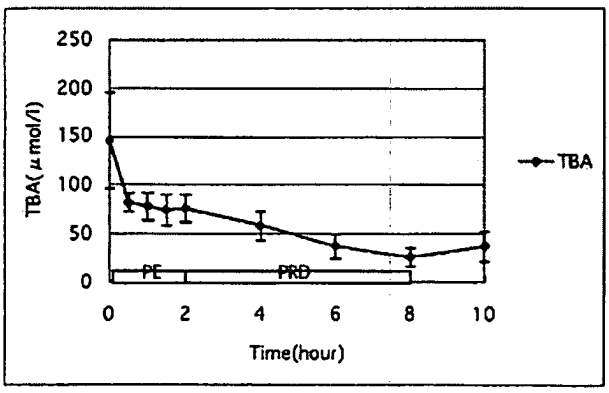
[図11]


50
40
30
20
10
0
Ht(%)
Ht
PE
PRD
0
2
4
6
8
10
Time(hour)

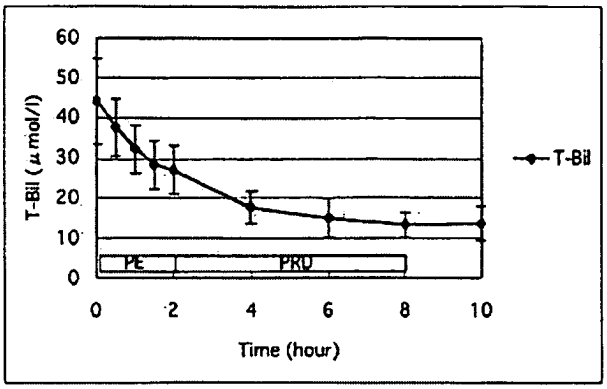
[図12]


120
100
80
60
40
20
0
Platelet(×10^4/μl)
Platelet
PE
PRD
0
2
4
6
8
10
Time(hour)

[図13]


250
200
150
100
50
0
TBA(μmol/l)
TBA
PE
PRD
0
2
4
6
8
10
Time(hour)

[図14]



INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2005/000825

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[7] A61M1/14, 1/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[7] A61M1/02-1/36

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Jitsuyo Shinan Koho	1922-1996	Jitsuyo Shinan Toroku Koho	1996-2005
Kokai Jitsuyo Shinan Koho	1971-2005	Toroku Jitsuyo Shinan Koho	1994-2005

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JP 9-507414 A (HemoCleanse, Inc.), 29 July, 1997 (29.07.97), Full text; all drawings & WO 95/18671 A & US 5536412 A	1-7,9,11
A	JP 7-506765 A (STANGE, Jan), 27 July, 1995 (27.07.95), Full text; all drawings & WO 94/21363 A	1-7,9,11

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search 09 February, 2005 (09.02.05)	Date of mailing of the international search report 01 March, 2005 (01.03.05)
Name and mailing address of the ISA/ Japanese Patent Office Facsimile No.	Authorized officer Telephone No.

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2005/000825

Box No. II **Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 8, 10
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
The subject matter of the inventions of claims 8 and 10 cannot be identified because although claims 8 and 10 contain the language "shown in Fig. 1", it is probable that drawings are interpreted in multisense.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III **Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

国際調査報告

国際出願番号 PCT/JP2005/000825

A. 発明の属する分野の分類（国際特許分類（IPC））

Int.Cl' A61M1/14, 1/34

B. 調査を行った分野

調査を行った最小限資料（国際特許分類（IPC））

Int.Cl' A61M1/02-1/36

最小限資料以外の資料で調査を行った分野に含まれるもの

日本国実用新案公報	1922－1996年
日本国公開実用新案公報	1971－2005年
日本国実用新案登録公報	1996－2005年
日本国登録実用新案公報	1994－2005年

国際調査で使用した電子データベース（データベースの名称、調査に使用した用語）

C. 関連すると認められる文献

引用文献のカテゴリー*	引用文献名 及び一部の箇所が関連するときは、その関連する箇所の表示	関連する請求の範囲の番号
X	JP 9-507414 A (ヘモクレンズ・インコーポレーテッド) 1997.07.29, 全文, 全図 & WO95/18671 A & US 5536412 A	1-7, 9, 11
A	JP 7-506765 A (スタンゲ, ヤン) 1995.07.27, 全文, 全図 & WO94/21363 A	1-7, 9, 11

☐ C欄の続きにも文献が列挙されている。

☐ パテントファミリーに関する別紙を参照。

＊ 引用文献のカテゴリー

「A」特に関連のある文献ではなく、一般的技術水準を示すもの

「E」国際出願日前の出願または特許であるが、国際出願日以後に公表されたもの

「L」優先権主張に疑義を提起する文献又は他の文献の発行日若しくは他の特別な理由を確立するために引用する文献（理由を付す）

「O」口頭による開示、使用、展示等に言及する文献

「P」国際出願日前で、かつ優先権の主張の基礎となる出願の日の後に公表された文献

「T」国際出願日又は優先日後に公表された文献であって出願と矛盾するものではなく、発明の原理又は理論の理解のために引用するもの

「X」特に関連のある文献であって、当該文献のみで発明の新規性又は進歩性がないと考えられるもの

「Y」特に関連のある文献であって、当該文献と他の1以上の文献との、当業者にとって自明である組合せによって進歩性がないと考えられるもの

「&」同一パテントファミリー文献

国際調査を完了した日 09.02.2005	国際調査報告の発送日 01.3.2005
国際調査機関の名称及びあて先 日本国特許庁（ISA/JP） 郵便番号100－8915 東京都千代田区霞が関三丁目4番3号	特許庁審査官（権限のある職員） 寺澤 忠司 電話番号 03－3581－1101 内線 3344
	3E 3323

国際調査報告

国際出願番号　PCT／JP2005／000825

第Ⅱ欄　請求の範囲の一部の調査ができないときの意見（第１ページの２の続き）

法第８条第３項（ＰＣＴ１７条(2)(a)）の規定により、この国際調査報告は次の理由により請求の範囲の一部について作成しなかった。

1．☐ 請求の範囲 _____ は、この国際調査機関が調査をすることを要しない対象に係るものである。
つまり、

2．☒ 請求の範囲 8,10 は、有意義な国際調査をすることができる程度まで所定の要件を満たしていない国際出願の部分に係るものである。つまり、
請求の範囲８、１０には「図１に示される」と記載されているが、図面は多義的に解釈される可能性があるから、請求の範囲８、１０に係る発明の内容を特定することができない。

3．☐ 請求の範囲 _____ は、従属請求の範囲であってＰＣＴ規則6.4(a)の第２文及び第３文の規定に従って記載されていない。

第Ⅲ欄　発明の単一性が欠如しているときの意見（第１ページの３の続き）

次に述べるようにこの国際出願に二以上の発明があるとこの国際調査機関は認めた。

1．☐ 出願人が必要な追加調査手数料をすべて期間内に納付したので、この国際調査報告は、すべての調査可能な請求の範囲について作成した。

2．☐ 追加調査手数料を要求するまでもなく、すべての調査可能な請求の範囲について調査することができたので、追加調査手数料の納付を求めなかった。

3．☐ 出願人が必要な追加調査手数料を一部のみしか期間内に納付しなかったので、この国際調査報告は、手数料の納付のあった次の請求の範囲のみについて作成した。

4．☐ 出願人が必要な追加調査手数料を期間内に納付しなかったので、この国際調査報告は、請求の範囲の最初に記載されている発明に係る次の請求の範囲について作成した。

追加調査手数料の異議の申立てに関する注意

☐ 追加調査手数料の納付と共に出願人から異議申立てがあった。

☐ 追加調査手数料の納付と共に出願人から異議申立てがなかった。